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(54) Title: SUBSTITUTED DIPEPTIDE ANALOGS PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

There are disclosed certain novel compounds identified as substituted dipeptide analogs which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such substituted dipeptide analogs as the active ingredient thereof are also disclosed.

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TITLE OF THE INVENTION

SUBSTITUTED DIPEPTIDE ANALOGS PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth

hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

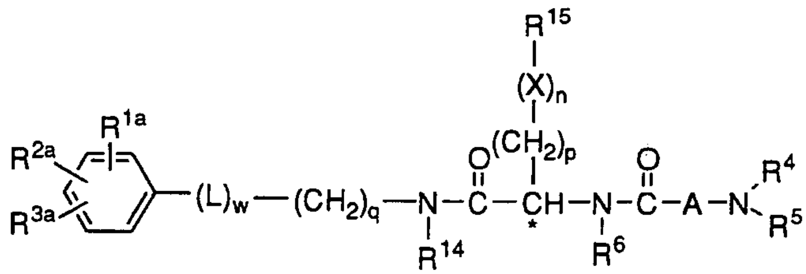
Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are highly substituted dipeptide analogs for promoting the release of growth hormone which are stable under various physiological conditions which may be administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

The instant invention covers certain substituted dipeptide analogs which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the diphenyl substituted dipeptide analogs. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the substituted dipeptide analogs for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

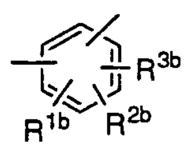
DESCRIPTION OF THE INVENTION

The novel substituted dipeptide analogs of the instant invention are best described in the following structural formula I:



I

where L is



n is 0 or 1;
p is 0 to 6;
q is 0 to 4;
w is 0 or 1;

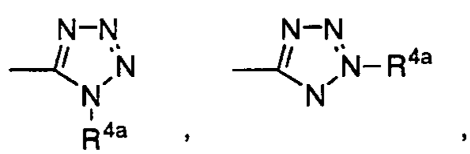
X is C=O, O, $S(O)_m$, $-\overset{\displaystyle OH}{\overset{|}{C}H}-$, $-\overset{\displaystyle R^{10}}{\overset{|}{N}}-$, -CH=CH-;
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_m-R^{7a}$, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO-(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, R^4R^5-$NCOO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy; R^{7a}

and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is



$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^{4b}R^{12c}N(CH_2)_v$-, $R^{12a}R^{12b}NCO(CH_2)_v$-, $R^{12a}R^{12b}NCS(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CO(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CS(CH_2)_v$-, $R^{4b}R^{12a}NCON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NCSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CON(R^{12c})(CH_2)_v$-,$R^{4b}R^{12a}NN(R^{12b})CSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})$-$COO(CH_2)_v$-, $R^{4b}R^{12a}NCOO(CH_2)_v$-, or $R^{13}OCON(R^{12c})(CH_2)_v$-, where v is 0 to 3;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12a} and R^{12c}, or R^{4b} and R^{12a}, or R^{4b} and R^{12a}, or R^{4b} and R^{12c}, or R^{13} and R^{12c}, can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3 and R^1 and R^{10} are as defined;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $-NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents

on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy where R^{10} and R^{11} are as defined;

R^{14} is hydrogen, R^1, R^2 independently disubstituted phenyl, C_1-C_{10} alkyl or substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl or $-NR^{10}R^{11}$ where R^1, R^2, R^{10} and R^{11} are as defined;

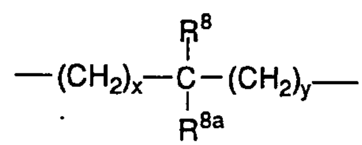
R^{15} is hydrogen, trifluoromethyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted naphthyl, C_3-C_7 cycloalkyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted naphthyl, R^1, R^2 independently disubstituted naphthyl C_1-C_3 alkoxy, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ or R^1, R^2 independently disubstituted heterocycle, where the heterocycle is imidazole, thiophene, furan, pyrrole, oxazole, thiazole, triazole, tetrazole, pyridine, benzofuran, benzothiophene, benzimidazole, indole, 7-azaindole, oxindole or indazole; where R^1, R^2, R^{10} and R^{11} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl,

C_1-C_5-alkoxycarbonyl, C_1-C_5-alkanoyl or C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B, r, s, R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-3;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or

branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention are realized when in the above structural formula:

n is 0 or 1;
p is 0 to 4;
q is 0 to 2;
w is 0 or 1;

X is O, $S(O)_m$, $-\overset{\displaystyle R^{10}\atop|}{N}-$, -CH=CH-;
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

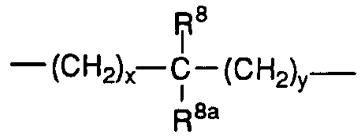
R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl or phenyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or $N-R^{10}$, r and s are independently 1 to 3 and R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Additional preferred compounds are realized in the above structural formula when:

n is 0 or 1;

p is 0 to 3;

q is 0 to 2;

w is 0 or 1;

X is O, $S(O)_m$ or -CH=CH-;

m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v-$, $R^{7b}COO(CH_2)_v-$, $R^{7b}OCO(CH_2)_v-$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a} or OR^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

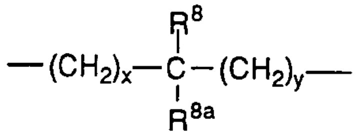
R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen or C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; or R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Still further preferred compounds of the instant invention are realized in the above structural formula when;
n is 0 or 1;
p is 0 to 2;
q is 1;
w is 1;
X is O, $S(O)_m$;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v-$, $R^{7b}COO(CH_2)_v-$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 or 1;

R^{3a} and R^{3b} are independently hydrogen, R^9, or C_1-C_6 alkyl substituted with R^9;

R^9 is as defined above;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined above;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20} alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen;

A is

$$-(CH_2)_x-\underset{R^{8a}}{\overset{R^{8}}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0-1;

R^8, R^{8a} and R^{8b} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

Representative preferred growth hormone releasing compounds of the present invention include the following:

1. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

2. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzene-butanamide

3. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

4. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

5. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenepentana-mide

6. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzene-pentanamide

7. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

8. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

9. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

10. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide

11. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

12. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

13. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

14. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenyl-methyl)oxy]propanamide

15. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

16. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

17. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide

18. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide

19. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide

20. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

21. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

22. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

23. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

24. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

25. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

26. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

27. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

28. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

29. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

30. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

31. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

32. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

33. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

34. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

35. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

36. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

37. (R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

38. (R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]-propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide

39. (R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]-oxy]propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide

40. (R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]-oxy]propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide

41. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

42. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

43. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

44. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

45. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

46. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

47. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

48. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

49. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

50. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

51. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

52. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

53. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

54. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide

55. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

56. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

57. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

58. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

59. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

60. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide

61. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

62. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

63. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

64. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

65. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-pentanamide

66. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzene-pentanamide

67. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

68. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

69. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

70. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

71. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

72. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

73. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

74. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

75. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

76. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

77. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

78. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

79. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

80. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]-propanamide

81. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

82. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide

83. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl]][1,1'-biphenyl]-4-yl]methyl]benzene-butanamide

84. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

85. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

86. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide

87. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzene-pentanamide

88. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]ben-zenepentanamide

89. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

90. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

91. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

92. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]amino]-methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

93. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide

94. (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide

95. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide

96. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbon-yl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide

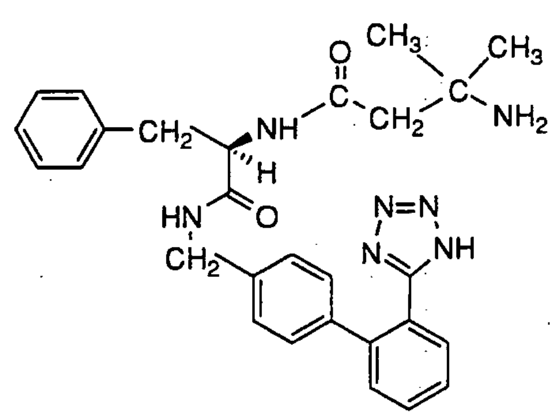
97. (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)-methyl]oxy]propanamide

98. (R)-α–[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propanamide

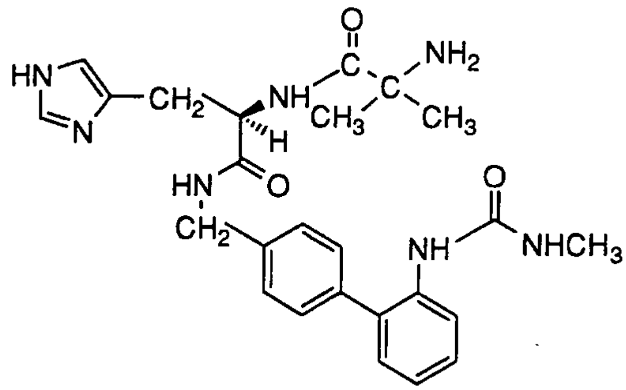
99. (R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

100. (R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

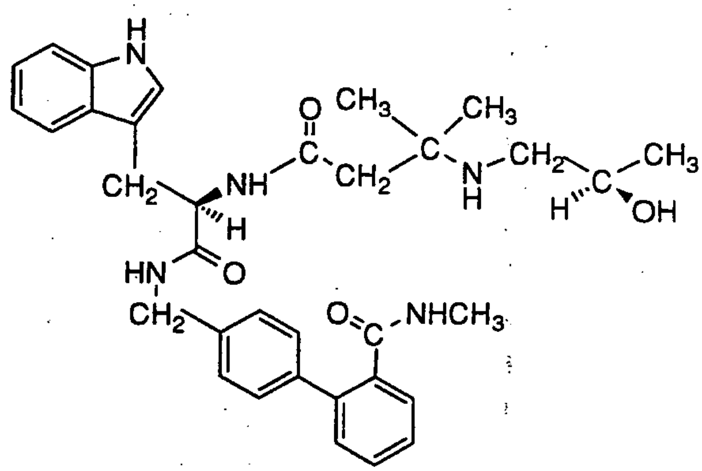
Representative examples of the nomenclature employed are given below:



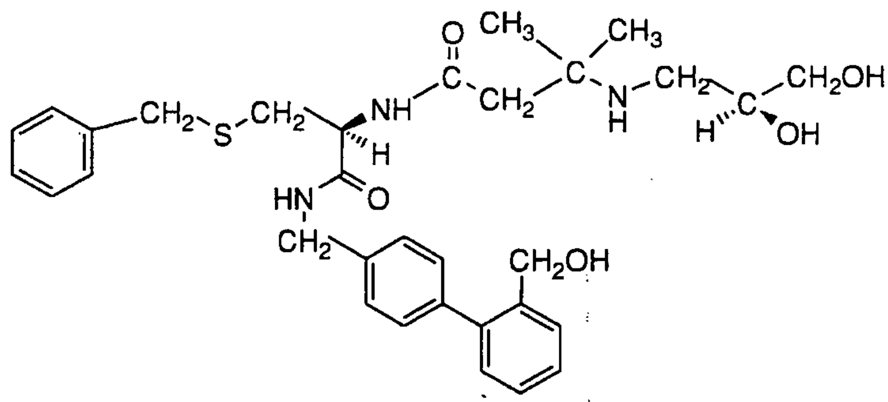
(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepropanamide



(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methyl-amino)carbonyl]amino][1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-4-yl-propanamide

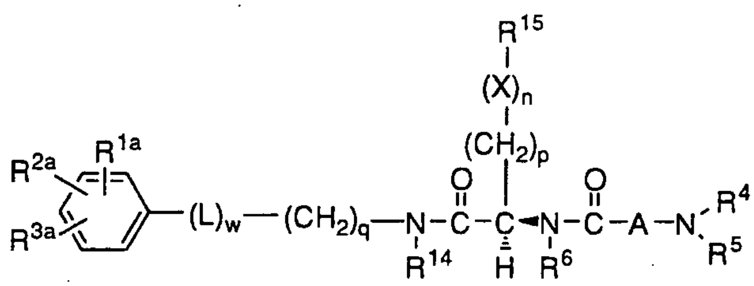


(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-methyl[1,1'-biphenyl]-2-carboxamide



(S)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-thio]propanamide

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the 3-amino substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the 3-amino substituent is below the plane of the structure. This center will be designated according to the R/S rules as either R or S depending upon the values of X, n, p and R15.



Ia

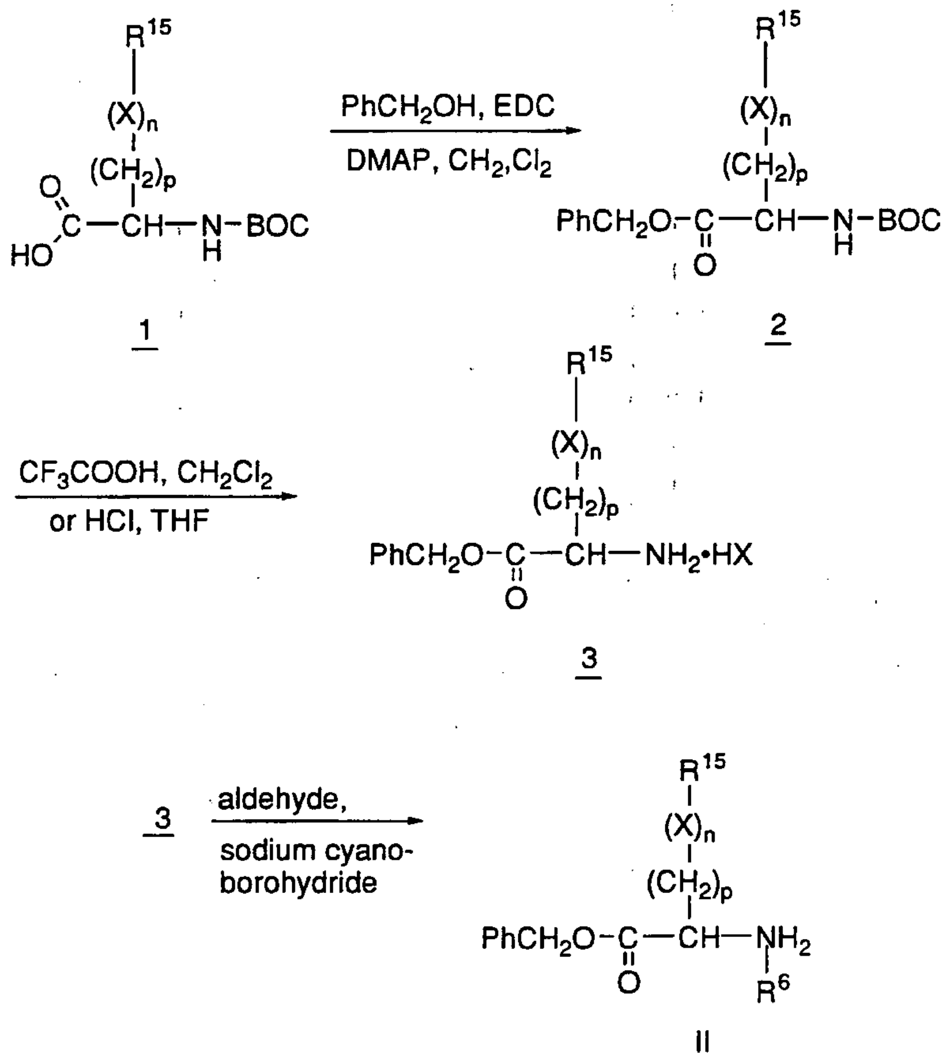
The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

Compounds I of the present invention are prepared from amino acid intermediates II as described in the following reaction schemes.

Amino acid intermediates 1 are, in some cases, commercially available in the form of their N-t-butoxycarbonyl or N-benzyloxycarbonyl derivatives. These intermediates can also be prepared by a variety of methods described in the literature and familiar to one skilled in the art. For example, the Strecker synthesis may be employed for the construction of racemic amino acid intermediates. Resolution can be achieved by classical methods, for example separation of diastereomeric salts by fractional crystallization. Alternatively, a chiral amino acid synthesis may be employed using the procedures described by R.M. Williams and M.N. Im (J. Amer. Chem. Soc., 113, 9276-9286, 1991.). Conversion of the free amino acid product to its N-t-butoxycarbonyl (BOC) derivative can be achieved by a number of methods known in the art, for example, treatment with di-

t-butyl dicarbonate in an inert solvent such as methylene chloride. Benzyloxycarbonyl (CBz) protected derivatives are obtained by treatment of the amino acid with, for example, benzyl chloroformate.

SCHEME 1

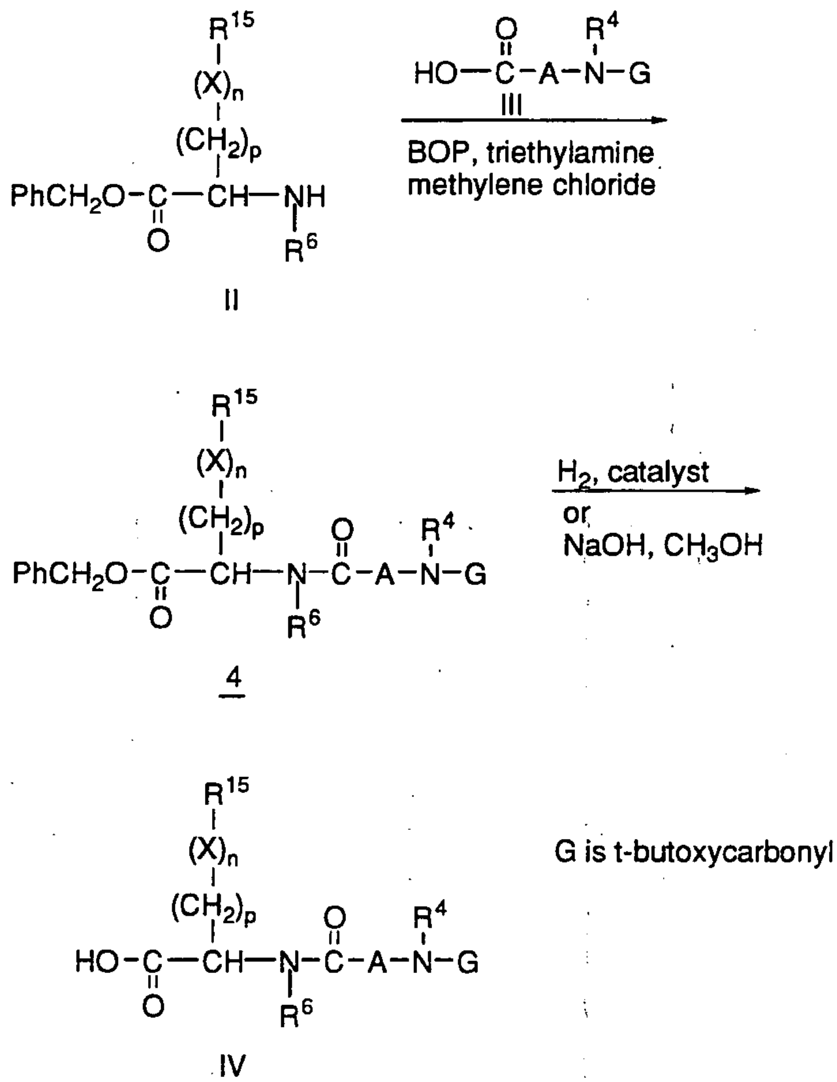


As shown in Scheme 1, formation of the benzyl ester $\underline{2}$ is carried out by treatment with benzyl alcohol in the presence of a coupling agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), in methylene chloride with a catalytic amount of

4-dimethylaminopyridine. Removal of the BOC protecting group through the use of trifluoroacetic acid in methylene chloride or hydrochloric acid in tetrahydrofuran gives the amine salt 3. Reductive alkylation with an aldehyde and a mild reducing agent, such as sodium cyanoborohydride, leads to the desired intermediate II.

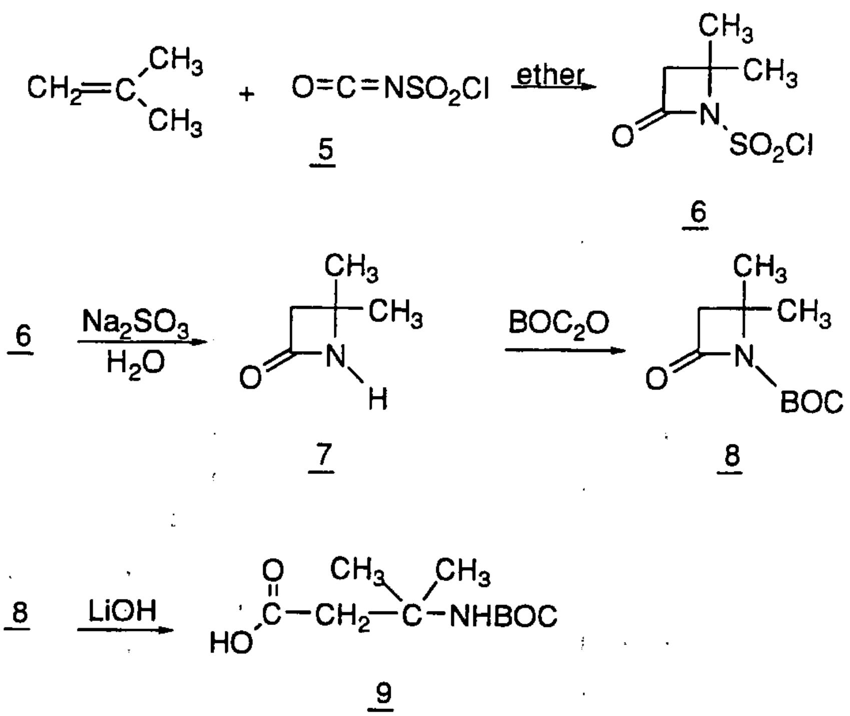
Attachment of the amino acid sidechain to intermediates of formula II is accomplished by the route shown in Scheme 2. Coupling is conveniently carried out by the use of an appropriately protected amino acid derivative, such as that illustrated by formula III, and a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978)) or by medium pressure liquid chromatography. Removal of the benzyl ester by hydrogenolysis or by saponification in the presence of a strong base, such as sodium hydroxide, affords the product IV. It may be appreciated by one skilled in the art that the protecting group G must be selected to be compatible with the conditions employed for removal of the specific class of ester present in 4. Hence, as illustrated for the benzyl ester 4, G is taken as t-butoxycarbonyl. It may further be appreciated that other combinations of protecting group G and ester functionality may be employed; for example, the benzyloxycarbonyl protecting group is inert to the standard conditions of aqueous sodium hydroxide employed to hydrolyze methyl or ethyl esters.

SCHEME 2



The protected amino acid derivatives III are, in many cases, commercially available in t-butoxycarbonyl (BOC) or benzyloxy-carbonyl (CBz) forms. A useful method to prepare the preferred sidechain 9 is shown in Scheme 3.

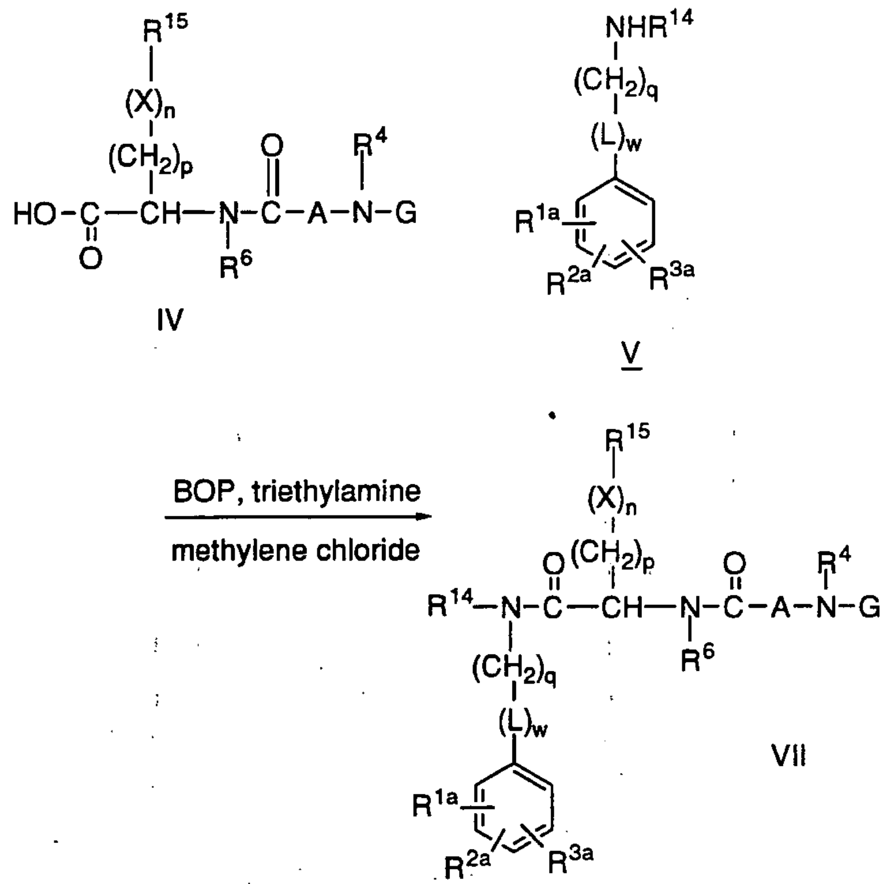
SCHEME 3



Reaction of isobutylene with N-chlorosulfonyl-isocyanate 5 in diethyl ether gives the azetidinone derivative 6. Removal of the chlorosulfonyl group with aqueous sodium sulfite followed by reaction with di-t-butyl-dicarbonate gives the BOC-protected intermediate 8. Alkaline hydrolysis gives the protected amino acid derivative 9 in good overall yield.

Attachment of the substituted phenyl sidechain V is achieved as shown in Scheme 4. Using the aforementioned BOP reagent, coupling is conveniently carried out in an inert solvent, such as methylene chloride, to give compounds of formula VII in protected form.

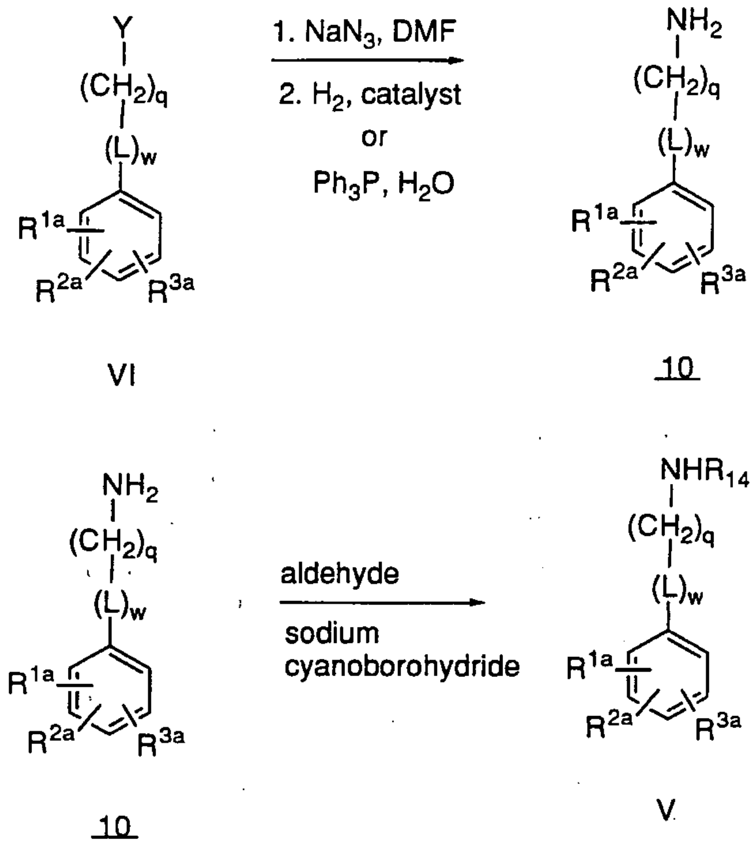
SCHEME 4



G is t-butoxycarbonyl or benzyloxycarbonyl

The substituted phenyl sidechains V are prepared from the corresponding alkylating agent VI by displacement of the leaving group Y with sodium azide as shown in Scheme 5. Reduction of the azide product by hydrogenation in the presence of a transition metal catalyst, or alternatively by reaction with triphenylphosphine followed by hydrolysis, gives the desired amine derivative 10. Conversion to the desired intermediate V is achieved by the aforementioned reductive alkylation procedure.

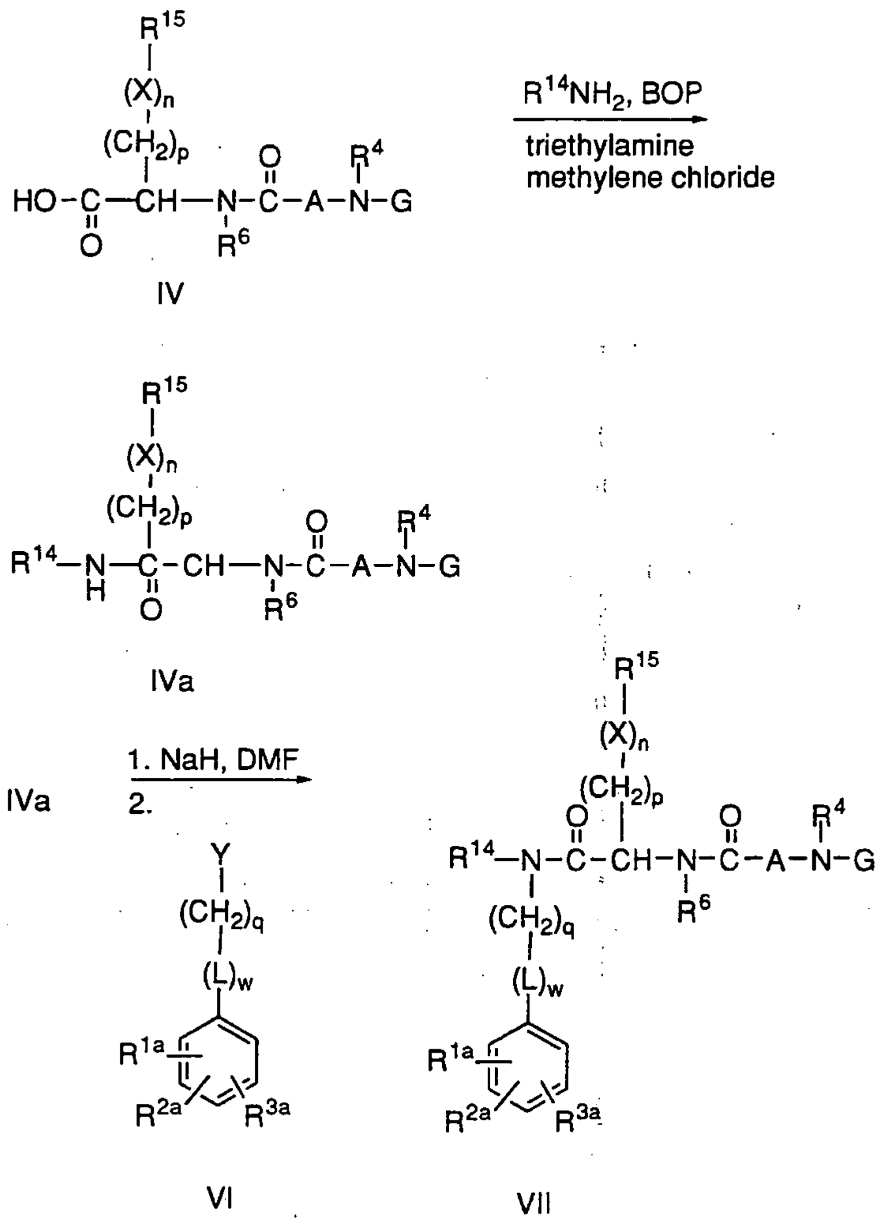
SCHEME 5



Y is a leaving group

As illustratrated in Scheme 6 an alternative route involves coupling of intermediate IV with $R^{14}NH_2$ using one of the coupling reagents described previously, followed by alkylation of the amide bond with VI. Alkylation is carried out in an inert solvent, such as dimethylformamide, using a strong base such as sodium hydride or potassium t-butoxide at temperatures of 0°-100°C. Alkylating agents VI are, in some cases, commercially available or may be prepared by the procedures described in the following schemes.

SCHEME 6

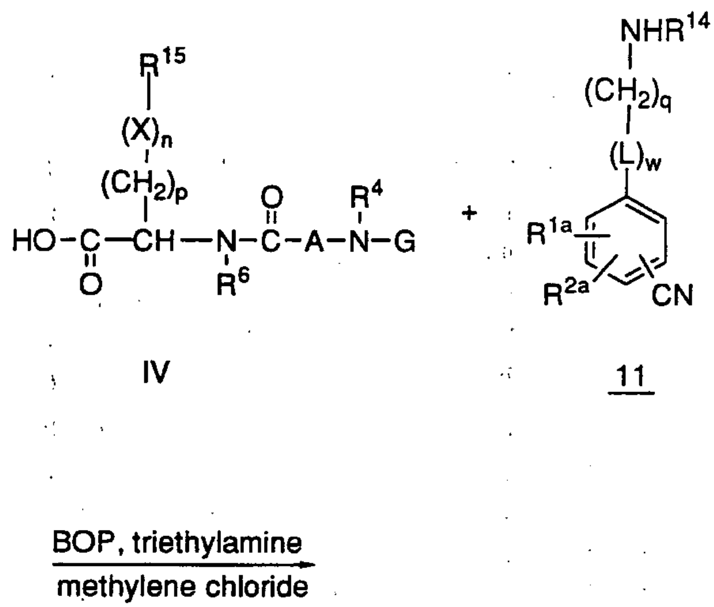


G is t-butoxycarbonyl or benzyloxycarbonyl

Alkylating agents VI are, in some cases commercially available compounds or may be prepared by methods described in the literature and familiar to one skilled in the art.

Compounds of formula I wherein R^{3a} or R^{3b} is a tetrazole (13) are prepared as described in Scheme 7 by reaction of IV with a suitably substituted intermediate 11 containing a nitrile as tetrazole precursor. Elaboration to the desired product 13 is carried out by treatment with trimethyltin azide in boiling toluene.

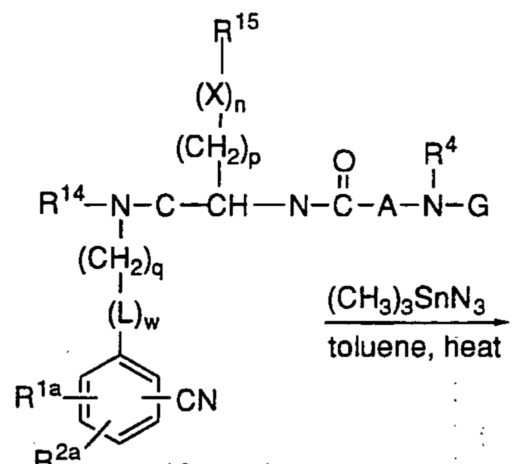
SCHEME 7



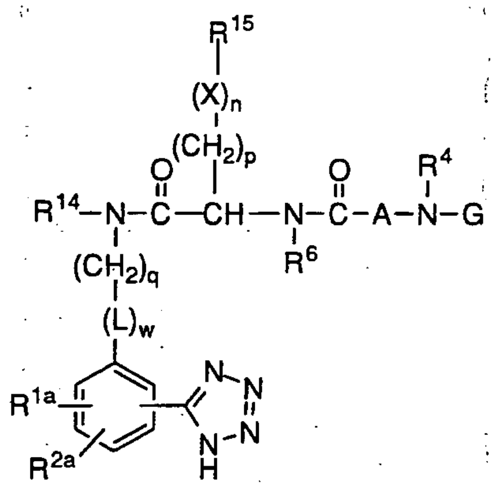
IV

11

SCHEME 7 (cont'd)



12

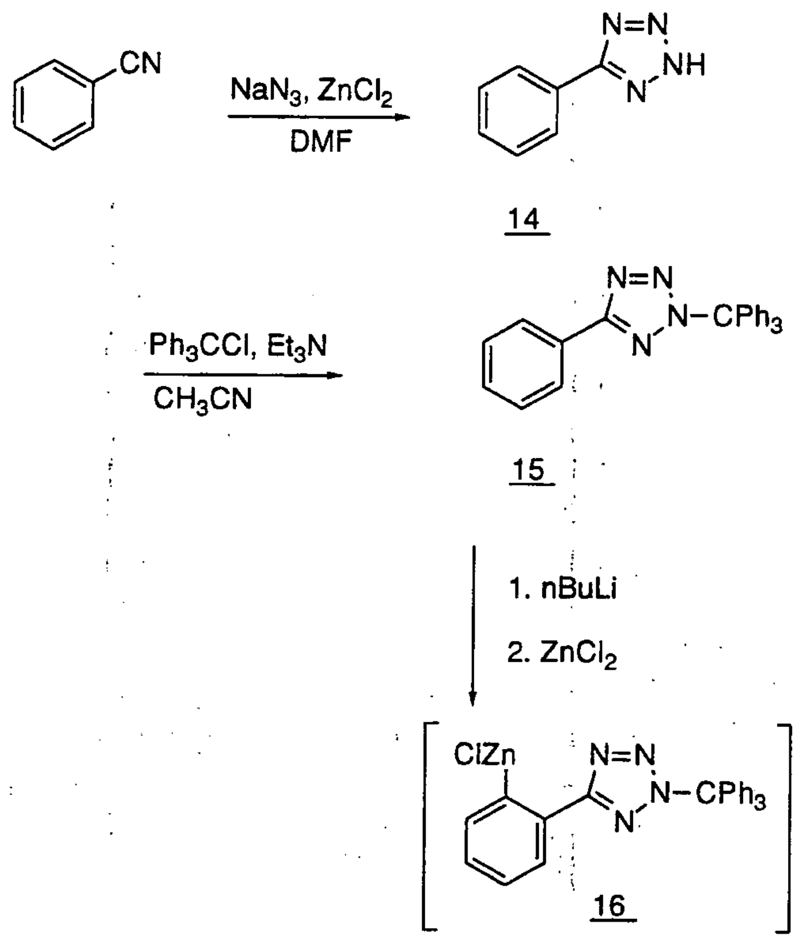


13

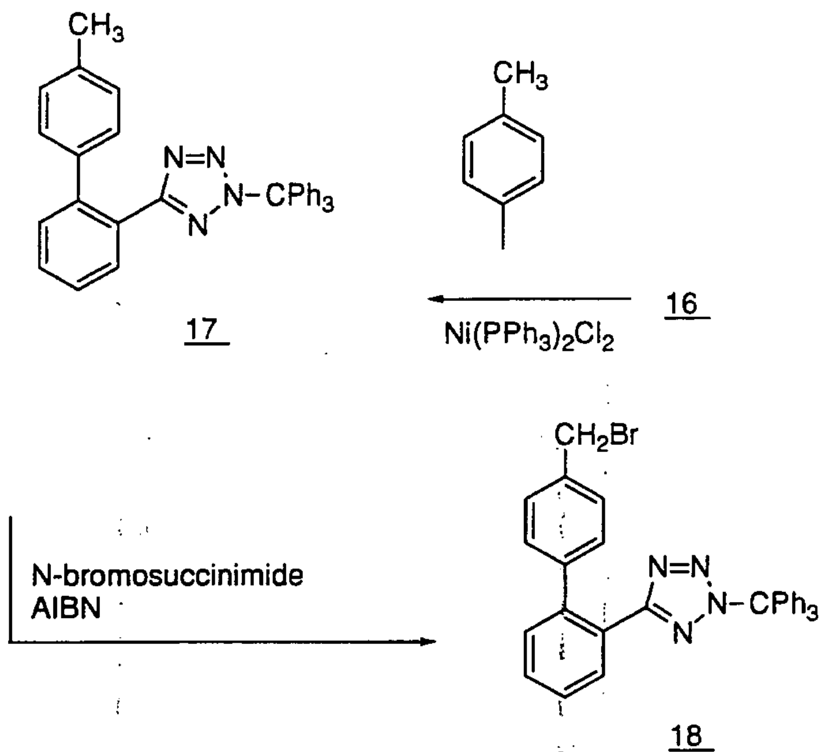
G=t-butoxycarbonyl or benzyloxycarbonyl

A useful method to prepare the preferred intermediate 18 is shown in Scheme 8, and in U.S. Patent 5,039,814.

SCHEME 8



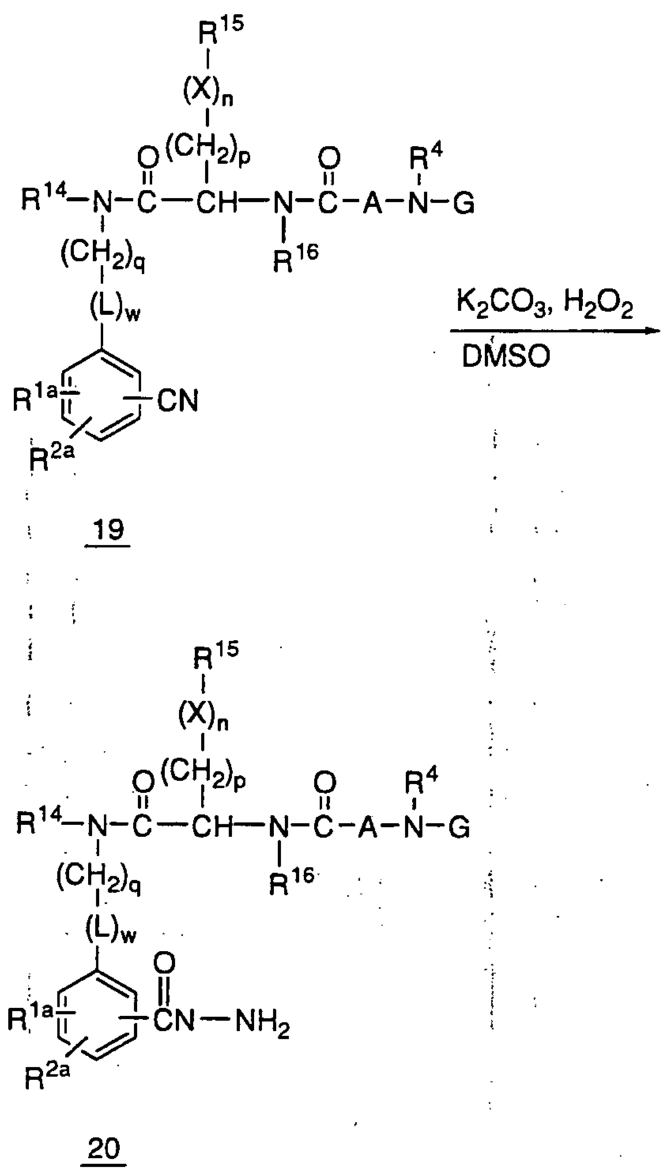
SCHEME 8 (cont'd)



As outlined in Scheme 8, benzonitrile is treated with sodium azide and zinc chloride to give 5-phenyltetrazole 14 which is converted to the N-trityl derivative 15 by treatment with triphenylmethyl chloride and triethylamine. The zinc reagent 16 was prepared by treatment with n-butyl lithium followed by zinc chloride. Coupling with 4-iodotoluene using the catalyst bis(triphenylphosphine)nickel(II) dichloride gives the biphenyl product 17 in high yield. Reaction with N-bromosuccinimide and AIBN gives bromide 18. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R^4R^5NCO can be prepared by several methods. For example, as shown in Scheme 9, compound 20 wherein R^4 and R^5 are both hydrogen is conveniently prepared by hydrolysis of a nitrile precursor 19.

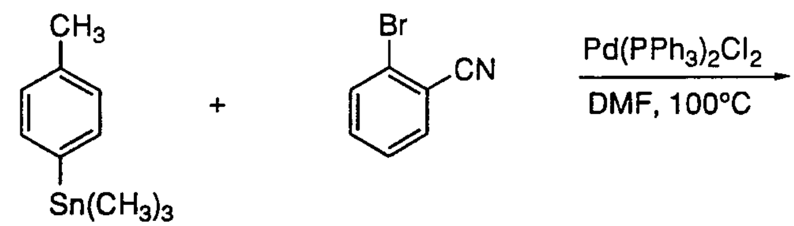
SCHEME 9



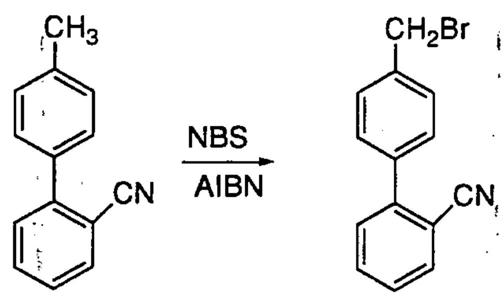
Thus, treatment of the nitrile 19 with hydrogen peroxide and a strong base, such as potassium carbonate, in a polar solvent, such as dimethylsulfoxide at temperatures of 25°C to 150°C results in formation of the amide derivative 20.

A useful method of preparing the intermediate 23 is outlined in Scheme 10.

SCHEME 10



21

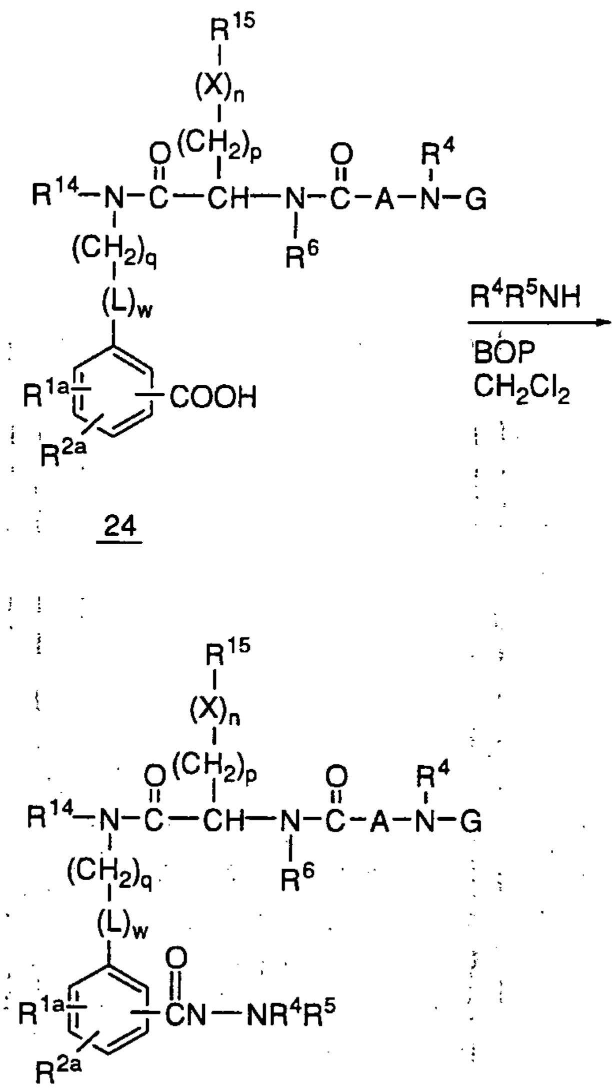


22 23

Thus, treatment of 4-(methylphenyl)trimethyl stannane 21 with 2-bromobenzonitrile in dimethylformamide at 100°C in the presence of bis-triphenylphosphine palladium (II) chloride results in coupling to form the biphenyl nitrile 22 in high yield. Conversion to bromide 23 is achieved by treatment with N-bromosuccinimide and a radical initiator, such as azobisisobutyronitrile (AIBN), in refluxing carbon tetrachloride. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R^4R^5NCO and R^4 and/or R^5 are other than hydrogen are prepared from the corresponding carboxylic acid derivatives 24 as shown in Scheme 11.

SCHEME 11

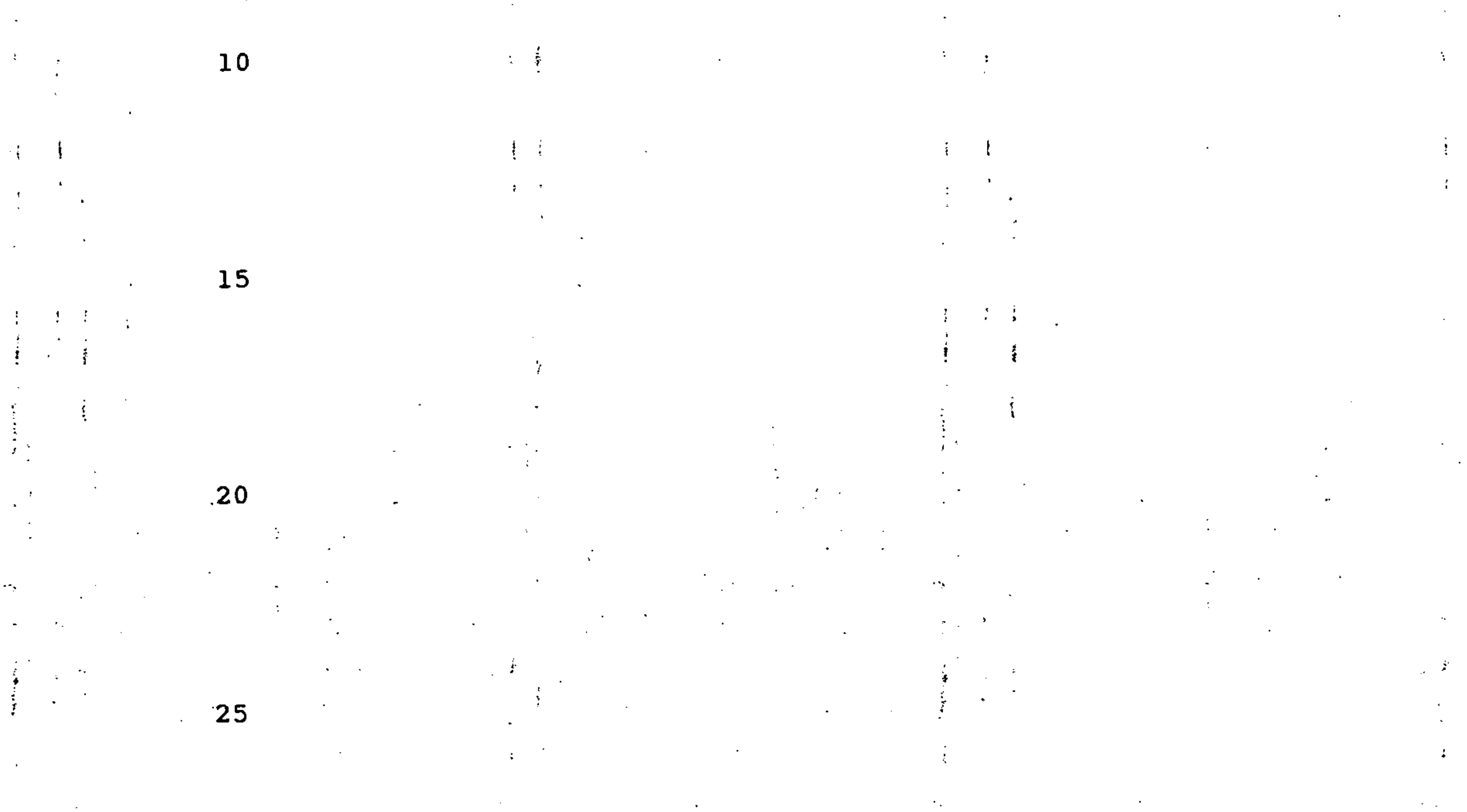


24

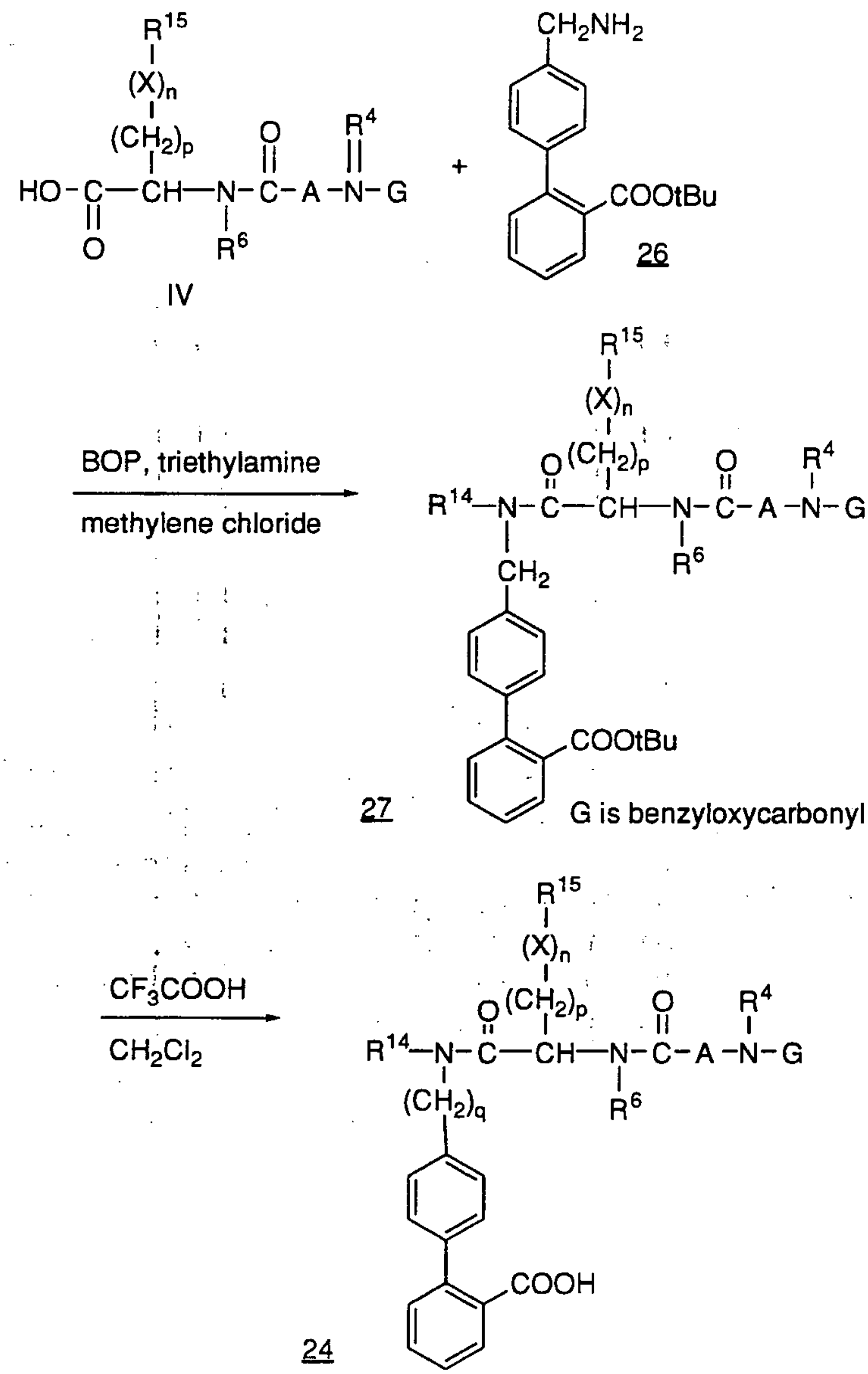
25

Coupling of the carboxylic acid derivative 24 with R^4R^5NH is conveniently carried out by the use of a coupling reagent such as benzotriazol-l-yloxytris-(dimethylamino)phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride.

The requisite carboxylic acid precursors can be prepared as illustrated in Scheme 12 for the biphenyl compound 24.

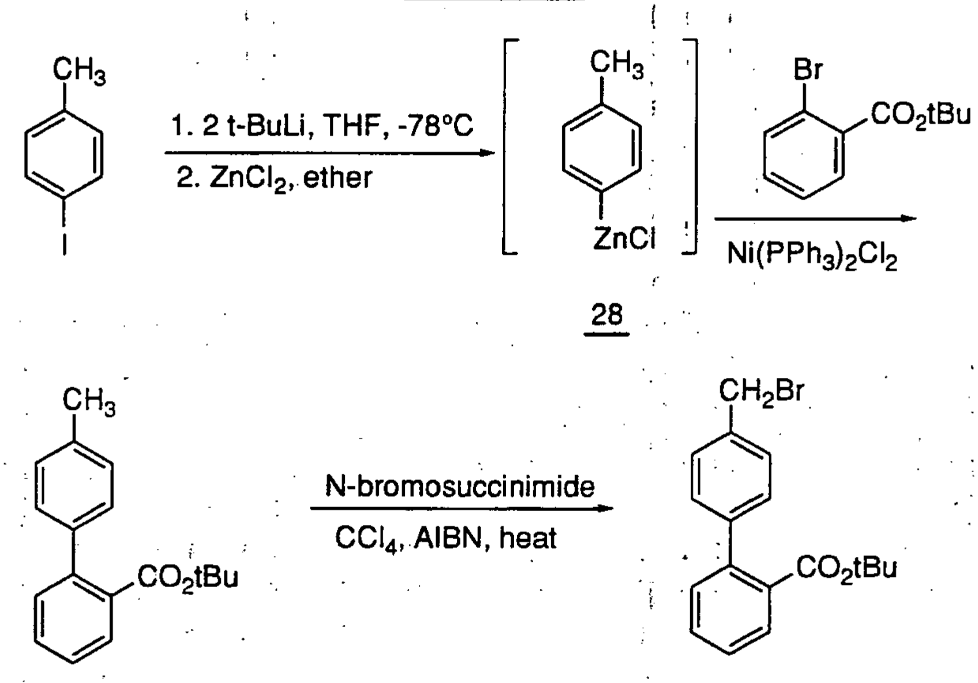


SCHEME 12


IV
26
BOP, triethylamine
methylene chloride
27
G is benzyloxycarbonyl
CF_3COOH
CH_2Cl_2
24

A convenient method to prepare the useful intermediate 30 is shown in Scheme 13. Metallation of 4-iodotoluene with t-butyl-lithium in tetrahydro-furan, followed by treatment with zinc chloride gives the intermediate zinc reagent 28. Coupling of 28 with t-butyl 2-bromobenzoate in the presence of bis(triphenylphosphine)nickel(II) chloride affords the biphenyl product 29 in high yield. Bromination to give the desired intermediate 30 is carried out under the aforementioned conditions. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

SCHEME 13



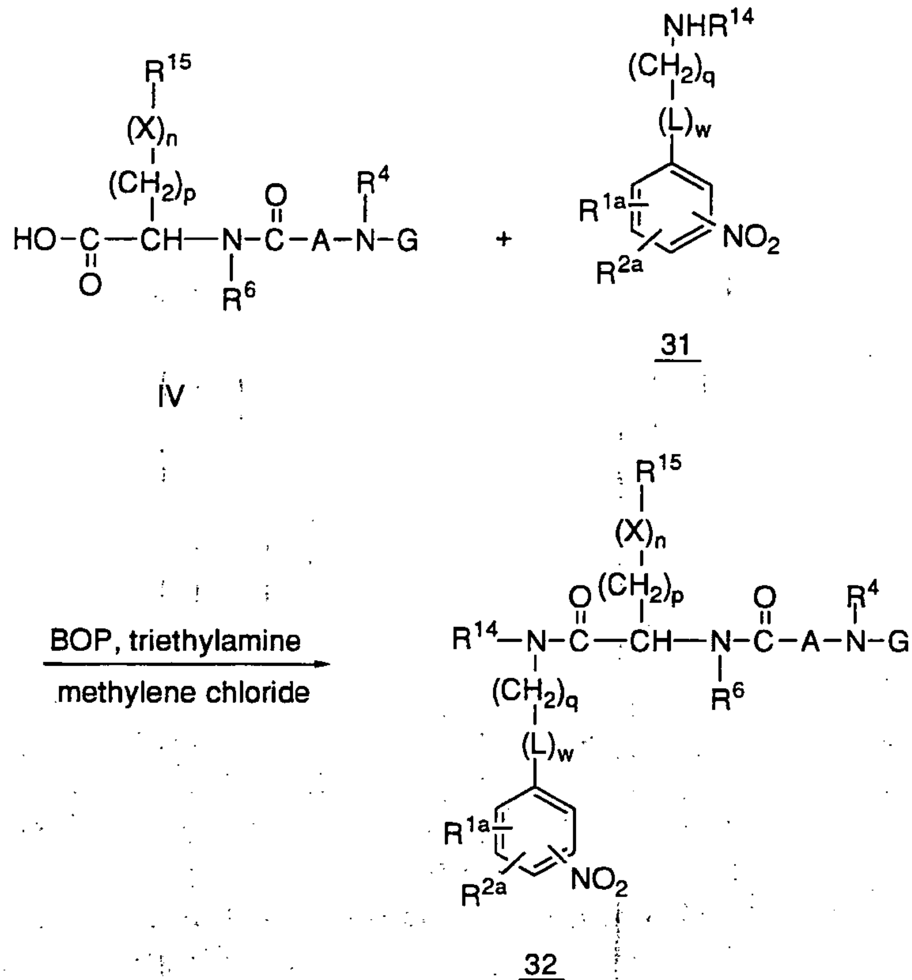
28

29

30

Compounds of formula I where R3a or R3b is a carbamate, semicarbazide or urea derivative, wherein this functionality is attached to the phenyl ring by a nitrogen atom are prepared from intermediate 32, obtained by reaction with a derivative 31 wherein R3a or R3b is a nitro group as shown in Scheme 14.

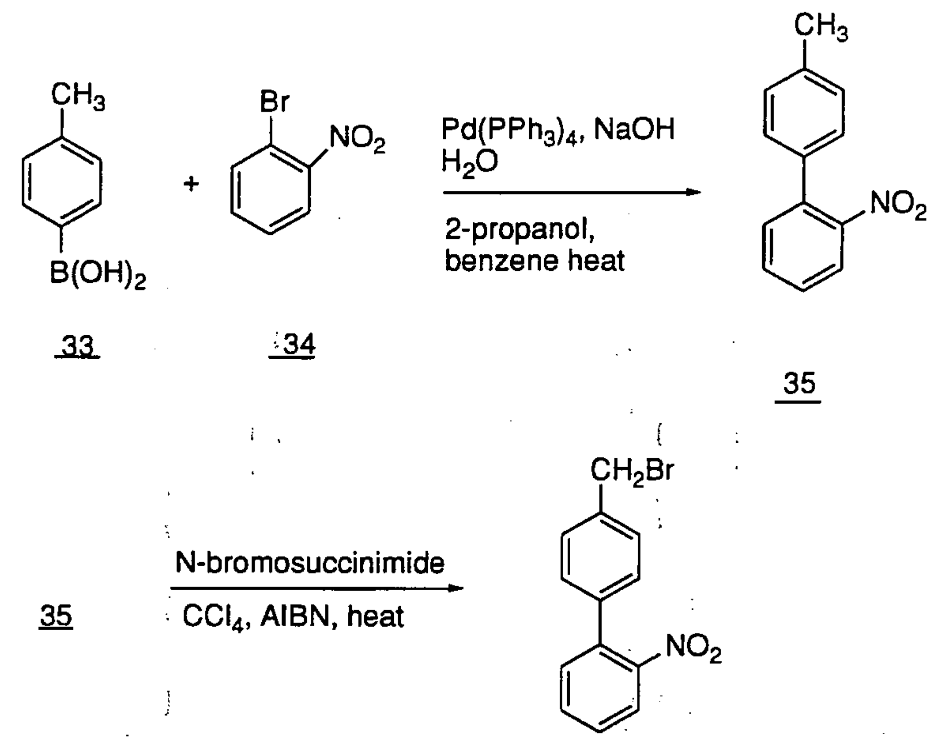
SCHEME 14



G is t-butoxycarbonyl

A useful method of synthesizing a preferred intermediate 36 is shown in reaction Scheme 15.

SCHEME 15



33 34 35

35

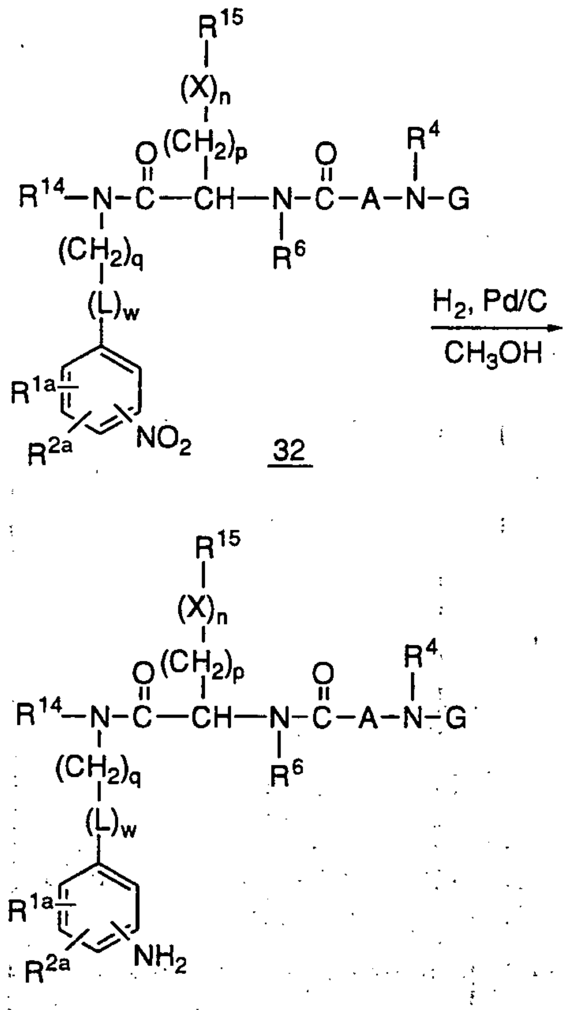
36

Reaction of 4-tolylboronic acid 33 with 2-bromo-nitrobenzene 34 in the presence of a transition metal catalyst such as (tetrakis)triphenylphosphine palladium (O) in a mixed solvent system containing aqueous sodium hydroxide, water, 2-propanol and benzene at elevated temperatures for several hours gives the coupled product 35 in good overall yield. Chromatographic purification and separation of unwanted by-products is conveniently performed on silica, eluting with common organic solvents such as hexane, ethyl acetate and methylene chloride. Conversion of 35 to the bromide derivative 36 is accomplished by treatment with N-bromosuccinimide in refluxing carbon tetrachloride in the presence of a radical initiator such as benzoyl peroxide or 2,2-azobisisobutyronitrile (AIBN). Conversion to

the requisite amine derivative V is acheived by the procedure described in Scheme 5.

As shown in Scheme 16, reduction of the nitro group of 32 is achieved by hydrogenation in the presence of a metal catalyst, such as palladium on carbon, in a protic solvent such as methanol or ethanol. It may be appreciated by one skilled in the art that for certain compounds where catalytic hydrogenation is incompatible with existing functionality, alternative methods of reduction are indicated, such as chemical reduction with stannous chloride under acidic conditions. It should also be noted that the protecting group G in intermediate 32 must be compatible with the experimental conditions anticipated for reduction. For example, intermediate 32 wherein G is t-butoxycarbonyl (BOC) are stable to the conditions of catalytic reduction employed in the conversion to 37. Intermediate 37 may also be further elaborated to new intermediate 38 by reductive alkylation with an aldehyde by the aforementioned procedures.

SCHEME 16

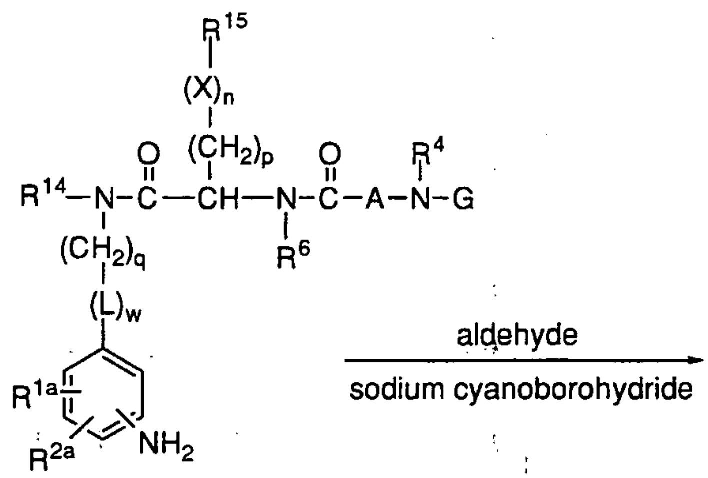


32

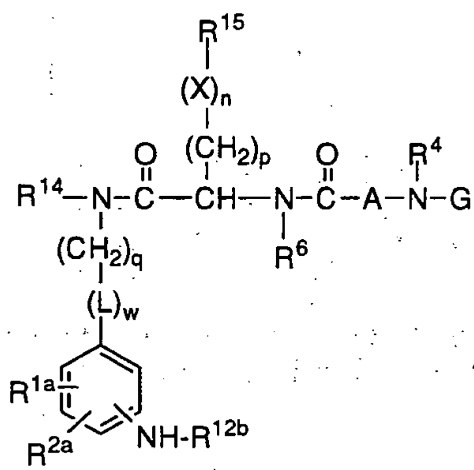
37

G is t-butoxycarbonyl

SCHEME 16 (cont'd)



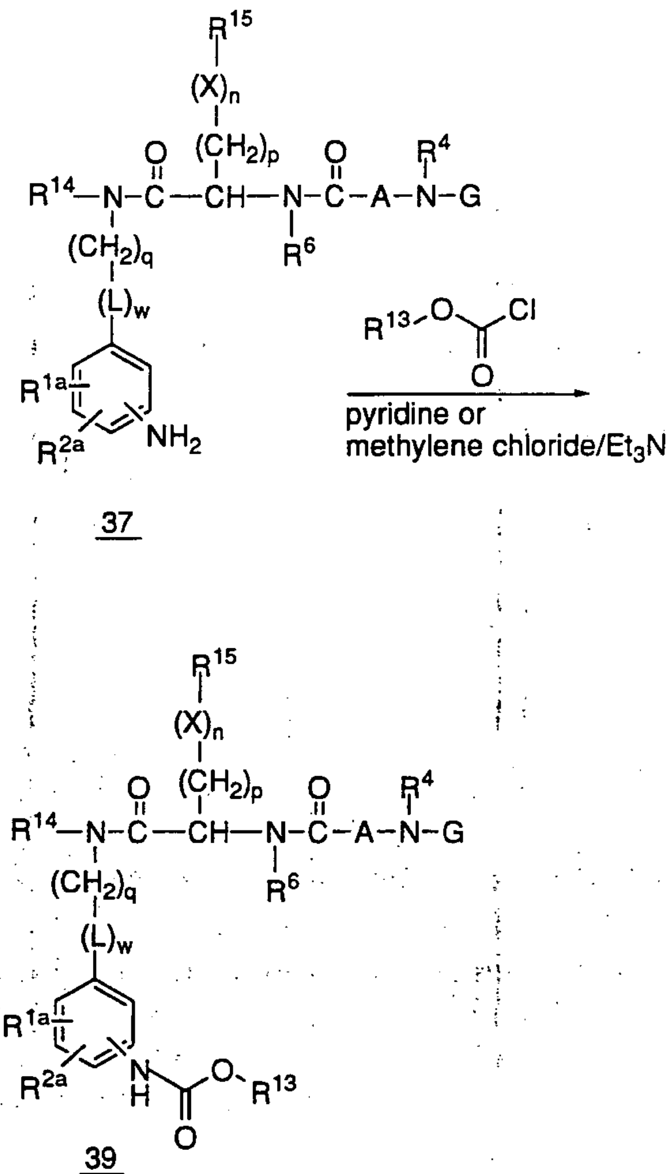
37



38 G is t-butoxycarbonyl

Elaboration of 37 to carbamate compounds is achieved by reaction with the appropriate chloroformate reagent in pyridine or in methylene chloride with triethylamine as shown in Scheme 17.

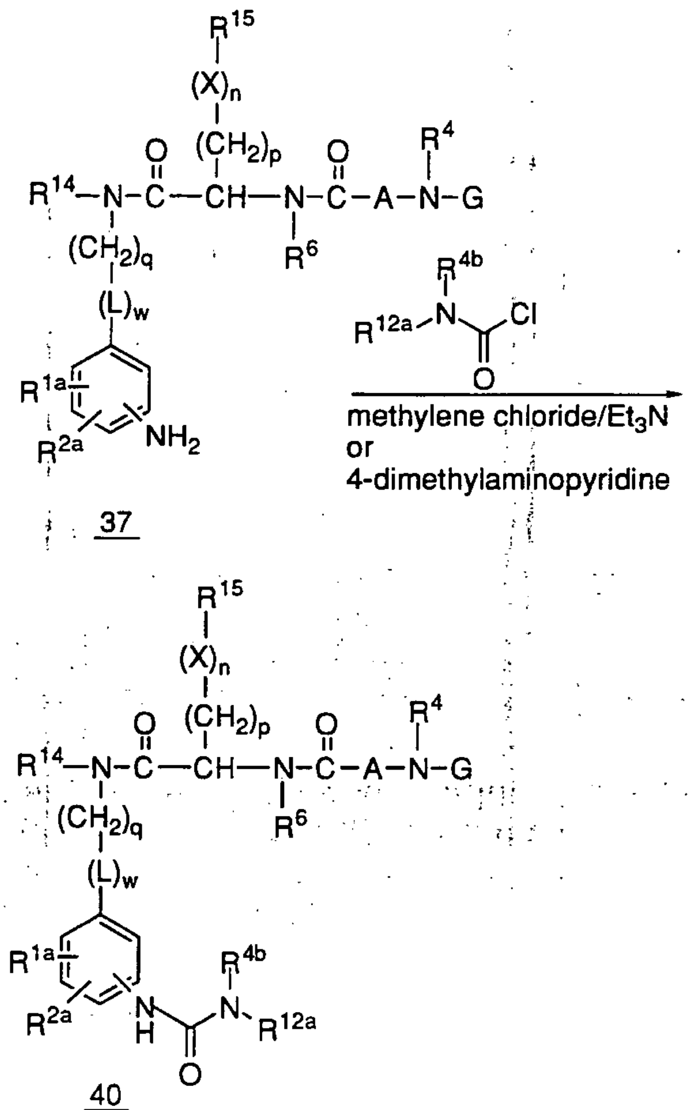
SCHEME 17



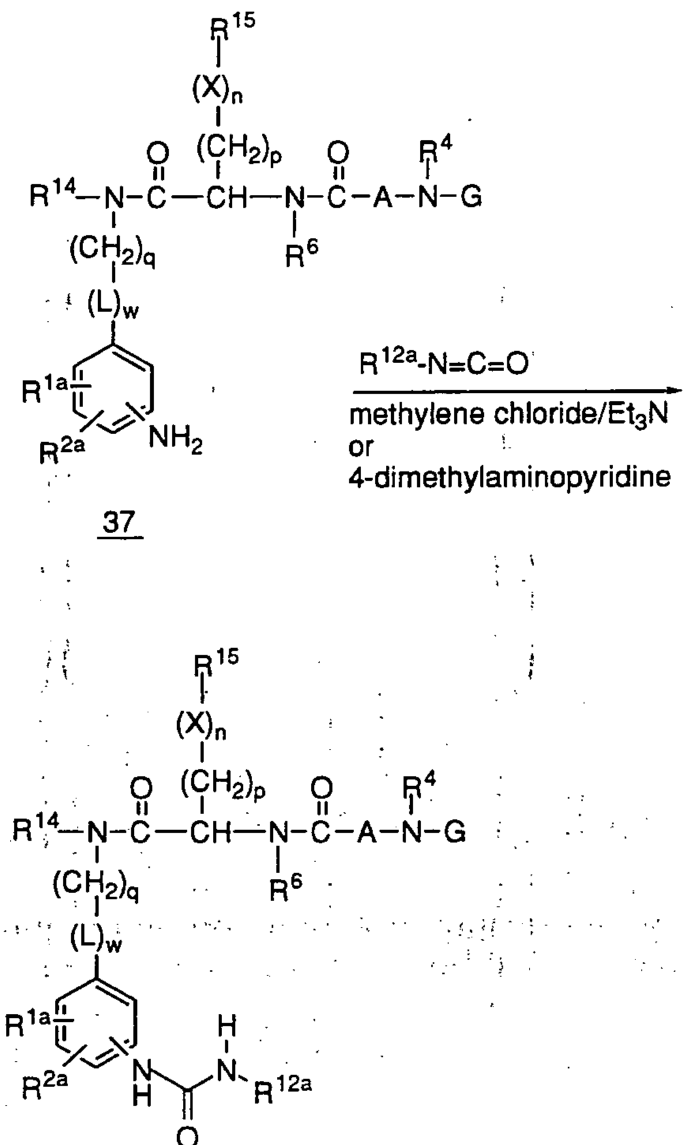
Transformation of amine intermediate 37 to urea derivatives is accomplished in several ways. Terminally disubstituted compounds 40 can be obtained directly by reaction of 37 with a disubstituted carbamoyl chloride in an inert solvent such as methylene chloride in the presence of triethylamine or 4-dimethylaminopyridine.

In addition, monosubstituted compounds 41 wherein either R^{4b} or R^{12a} is hydrogen are obtained from 37 by reaction with an isocyanate as shown in Scheme 18.

SCHEME 18



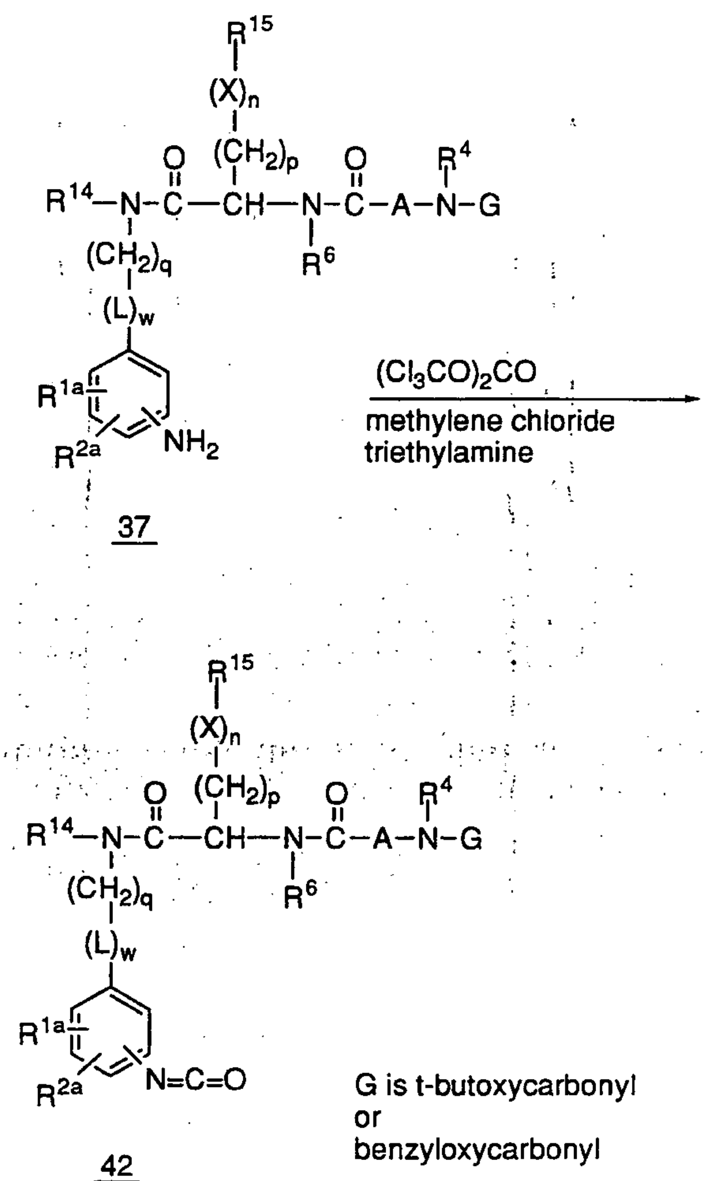
SCHEME 18 (cont'd)



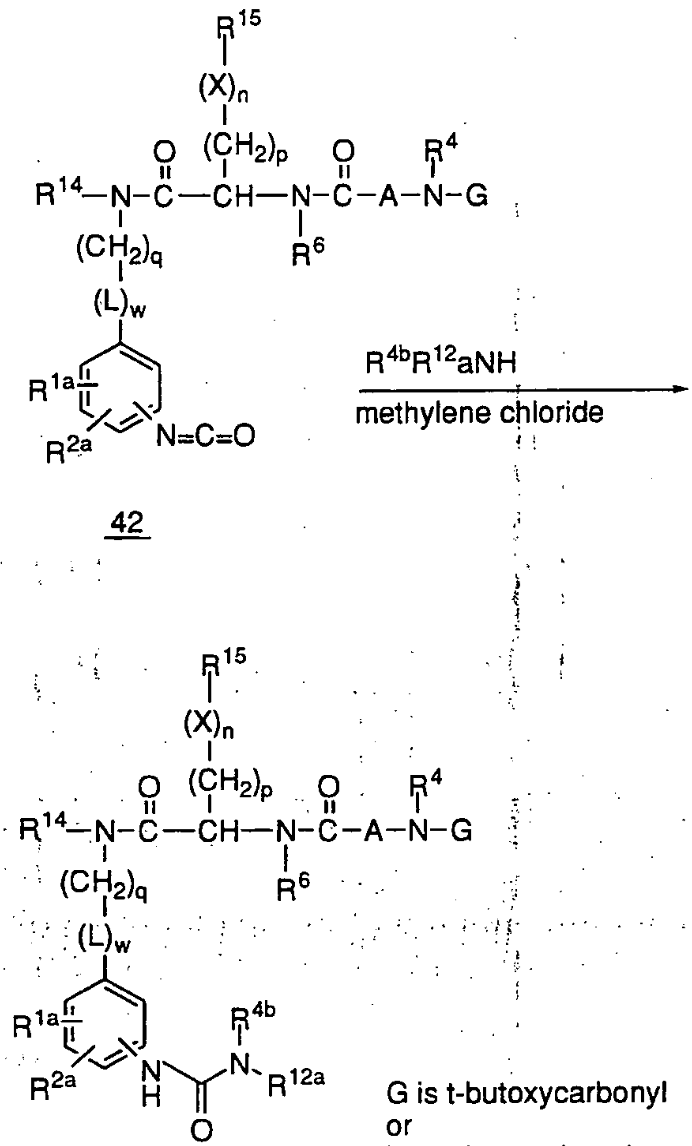
Alternatively, amine 37 is converted to an isocyanate 42 by treatment with phosgene or an equivalent reagent such as bis(trichloromethyl)carbonate (triphosgene) as indicated in Scheme 19. Subsequent reaction of 42 with primary or secondary amines in an inert solvent

such as methylene chloride gives the corresponding urea derivates 43 in good yield. Isocyanate 42 is also converted to substituted semi-carbazides 44 or hydroxy- or alkoxyureas 45 by reaction with substituted hydrazines or hydroxy- or alkoxylamines, respectively.

SCHEME 19



SCHEME 19 (cont'd)

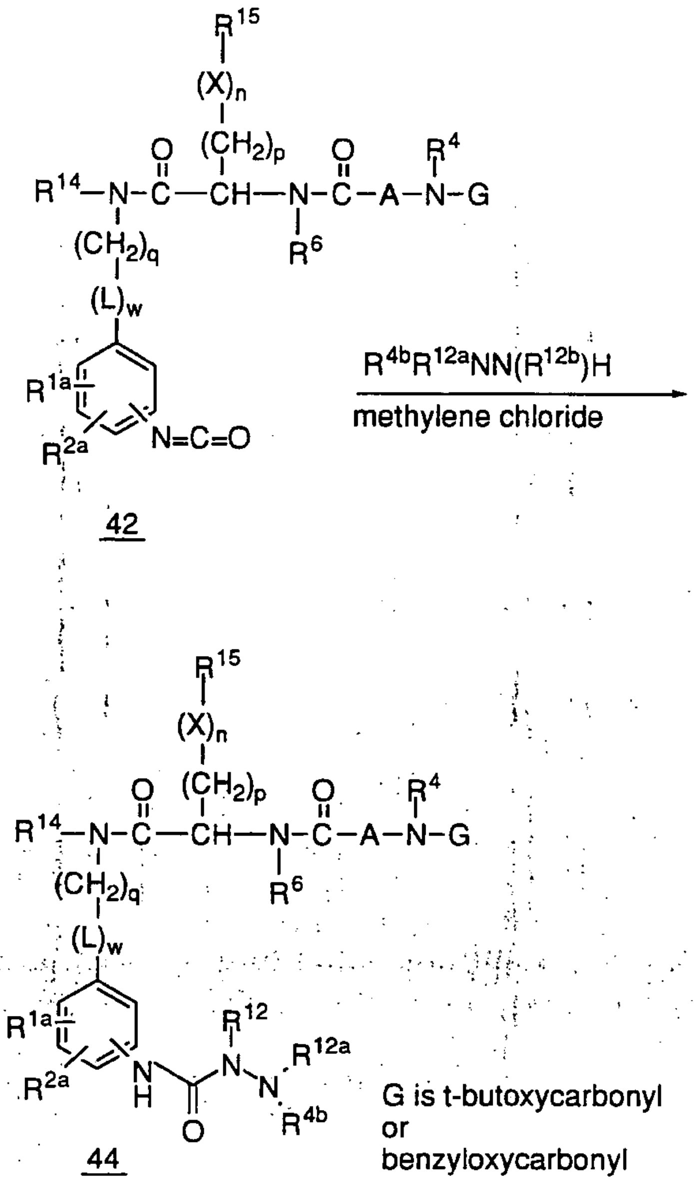


42

43

G is t-butoxycarbonyl or benzyloxycarbonyl

SCHEME 19 (cont'd)

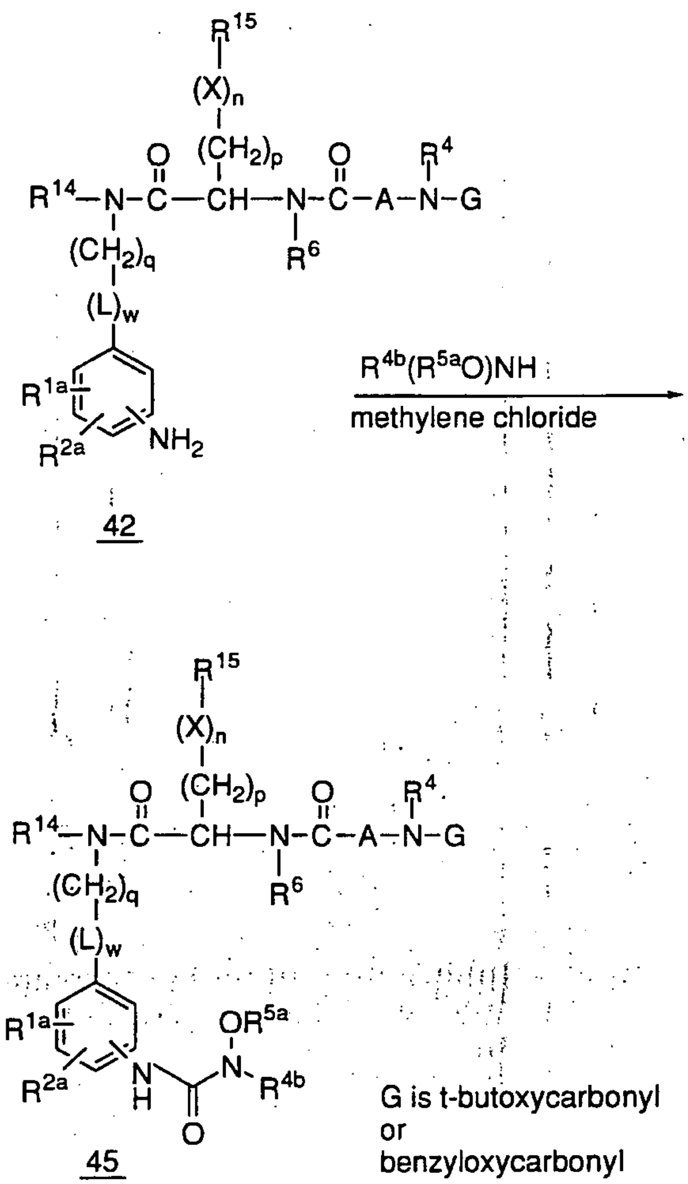


42

44

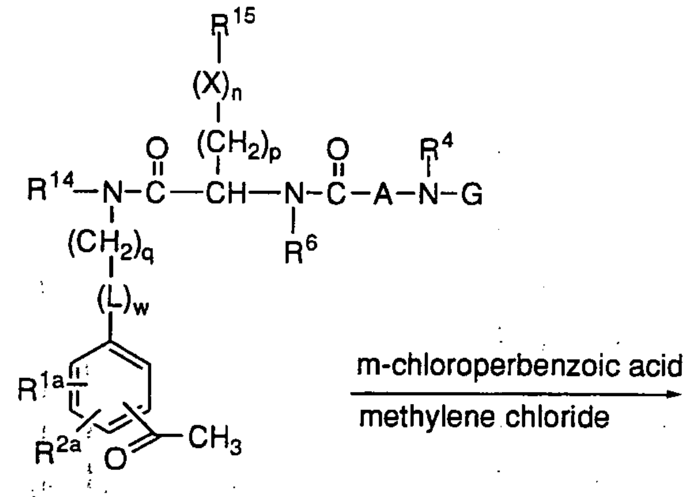
G is t-butoxycarbonyl or benzyloxycarbonyl

SCHEME 19 (cont'd)

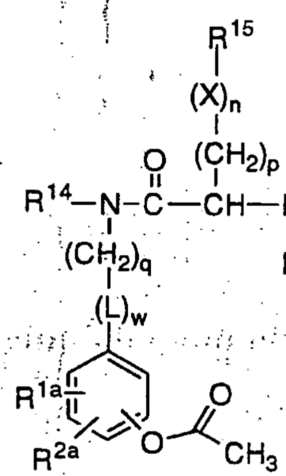


Compounds of formula I where R^{3a} or R^{3b} is a carbazate or carbamate derivative where attachment to the phenyl ring is through the oxygen atom of the carbazate or carbamate linkage are prepared from acetophenone intermediates 46 as indicated in Scheme 20.

SCHEME 20

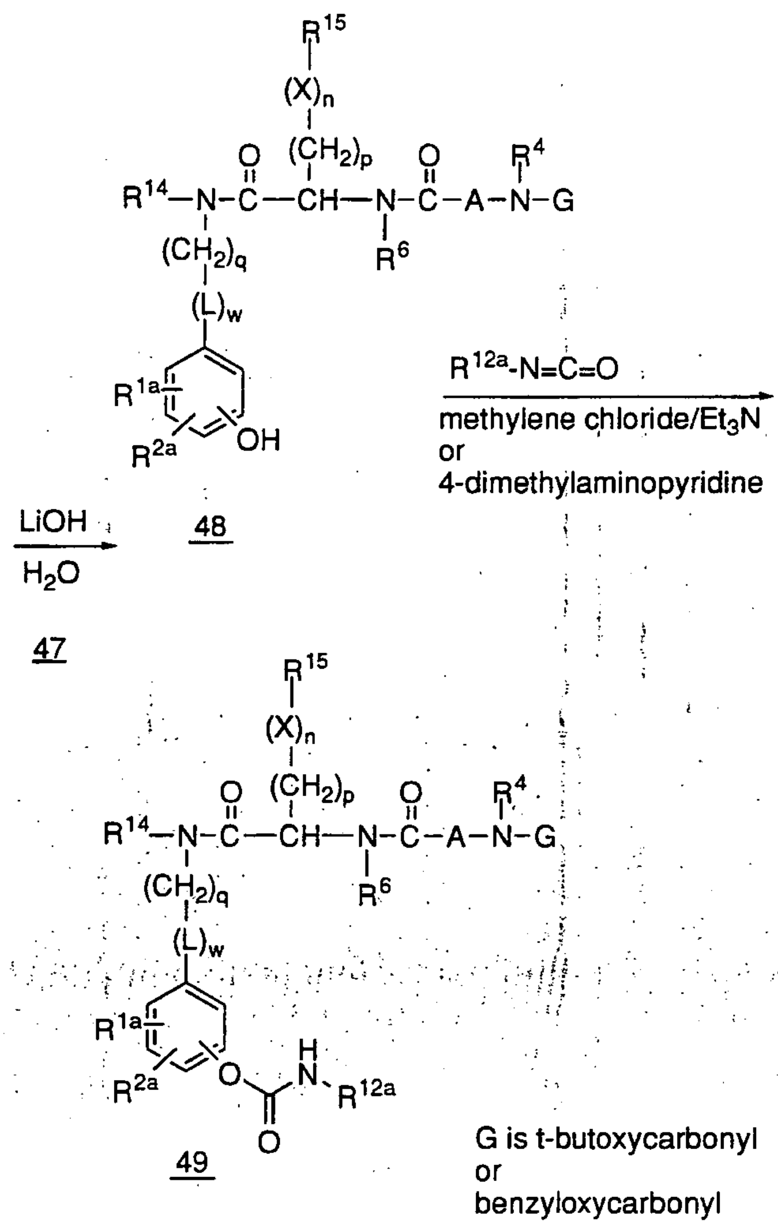


46

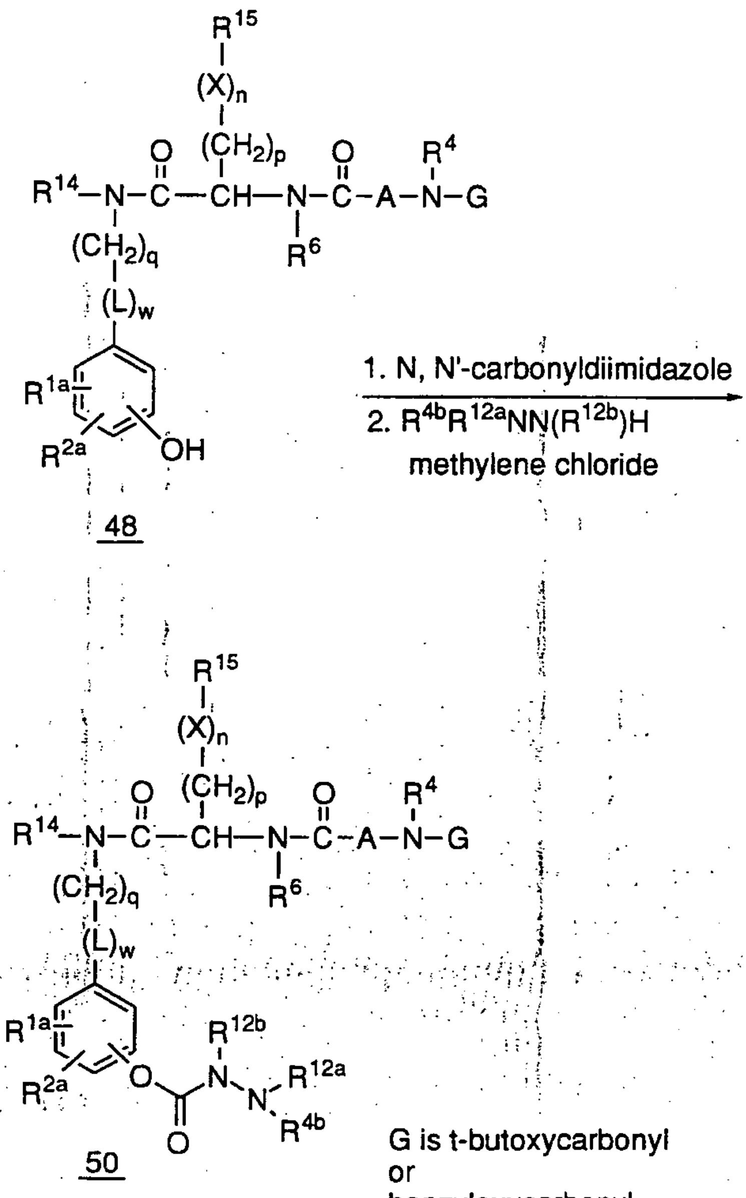


47

SCHEME 20 (cont'd)



SCHEME 20 (cont'd)



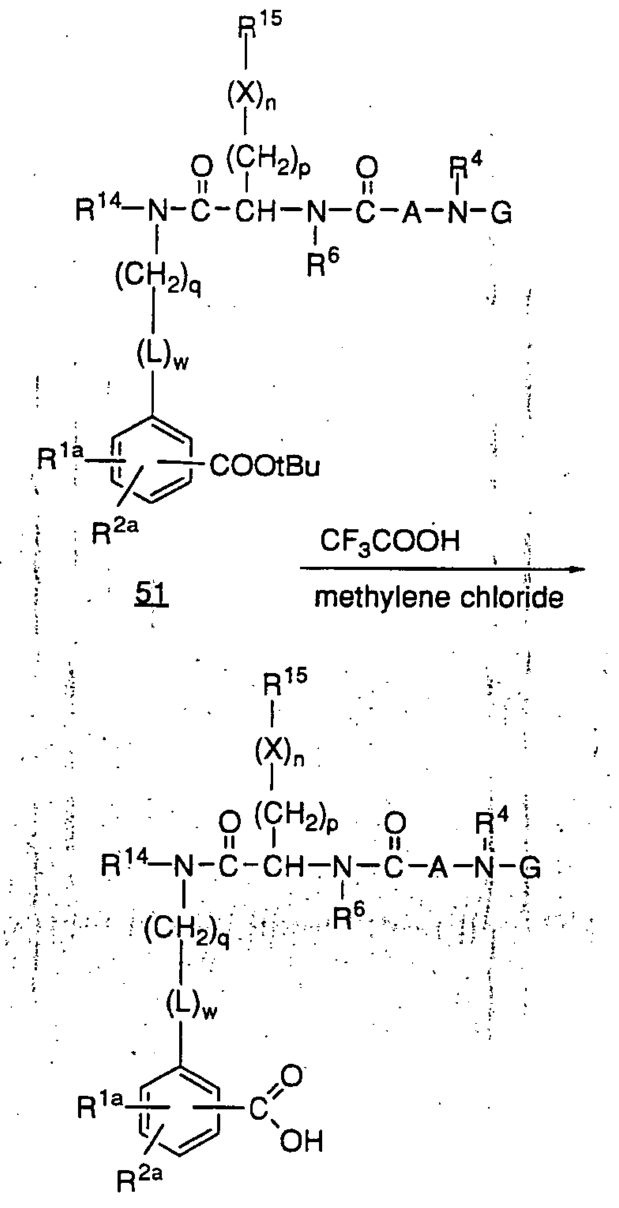
G is t-butoxycarbonyl or benzyloxycarbonyl

Oxidative rearrangement of 46 through the use of a peroxy-carboxylic acid (Baeyer-Villager reaction) such as m-chloroperbenzoic acid gives the ester 47 which is hydrolyzed in the presence of a strong base such as sodium or lithium hydroxide to give phenol 48.

Reaction of <u>48</u> with an isocyanate leads directly to carbamate analogs <u>49</u>. Additionally, treatment of <u>48</u> with N,N'-carbonyldiimidazole in dimethylformamide can form an activated intermediate which will react with substituted hydrazine reagents to give carbazate products <u>50</u>.

Compounds of formula I wherein R^{3a} or R^{3b} contains the linkage $-CH_2N(R^{12b})-$ can be prepared from the t-butyl ester intermediate <u>51</u> as described in Scheme 21. Removal of the t-butyl ester through the use of trifluoroacetic acid gives the carboxylic acid <u>24</u>. It may be appreciated by one skilled in the art that the protecting group G in <u>51</u> must therefore be compatible with the strongly acidic conditions employed for ester cleavage, hence G is taken as benzyloxycarbonyl. Conversion of the carboxylic acid to the benzylamine derivative <u>52</u> can be achieved by a five-step sequence consisting of: 1) formation of a mixed anhydride with isobutyl chloroformate; 2) reduction with sodium borohydride to the benzyl alcohol; 3) formation of the mesylate with methanesulfonyl chloride; 4) formation of the azide by reaction with sodium azide, and finally, 5) reduction of the azide with tin(II) chloride. The benzylamine intermediate <u>52</u> can be further elaborated to <u>53</u> by the aforementioned reductive amination procedure.

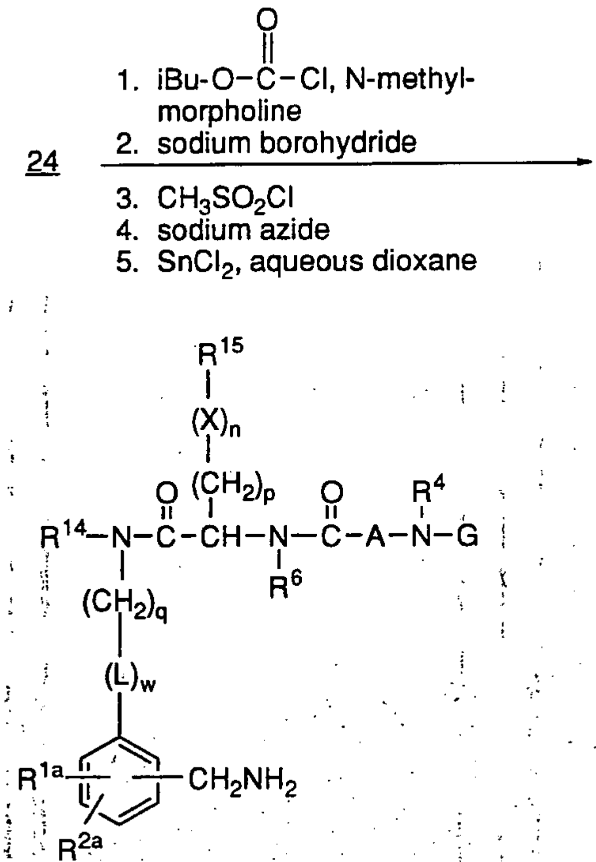
SCHEME 21



24 G is benzyloxycarbonyl

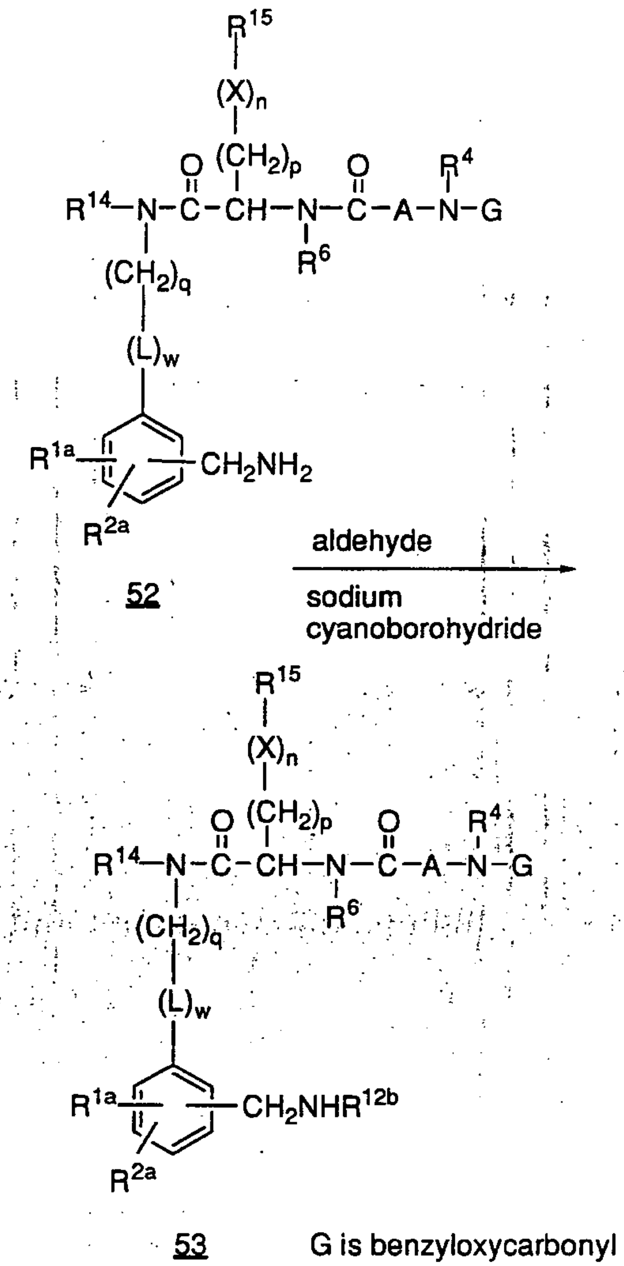
SCHEME 21 (Cont'd)

24



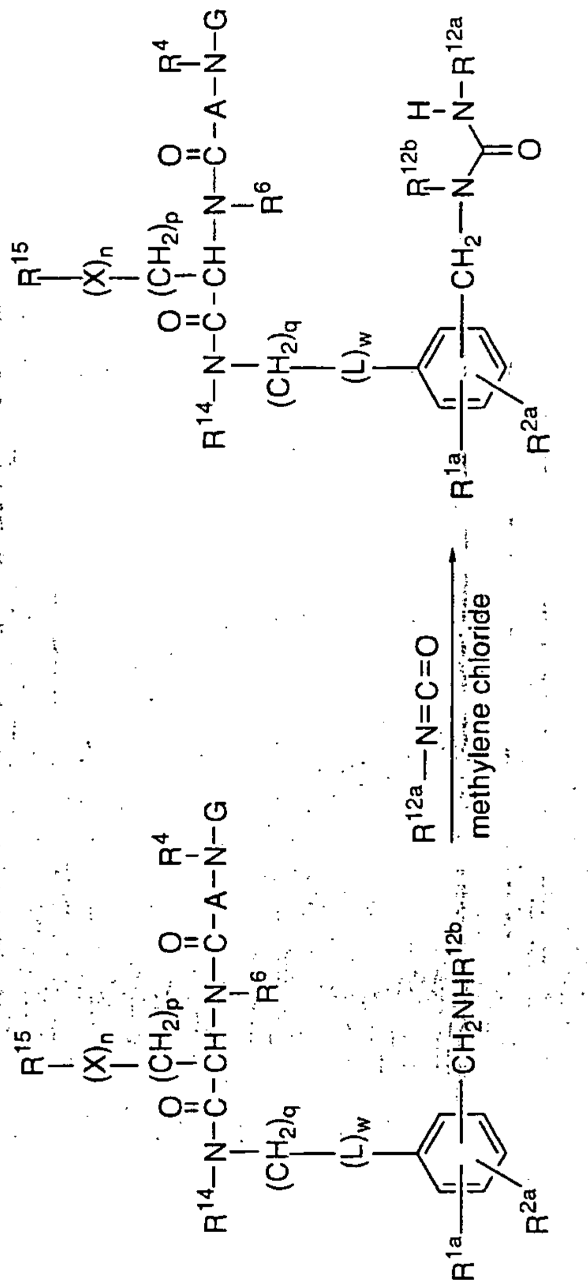
52 G is benzyloxycarbonyl

SCHEME 21 (Cont'd)



Reaction of amine 53 with the appropriate reagents to form urea-linked compounds 54 and 55 carbamate-linked compounds 56, and amide-linked structures 57 are illustrated in Scheme 22.

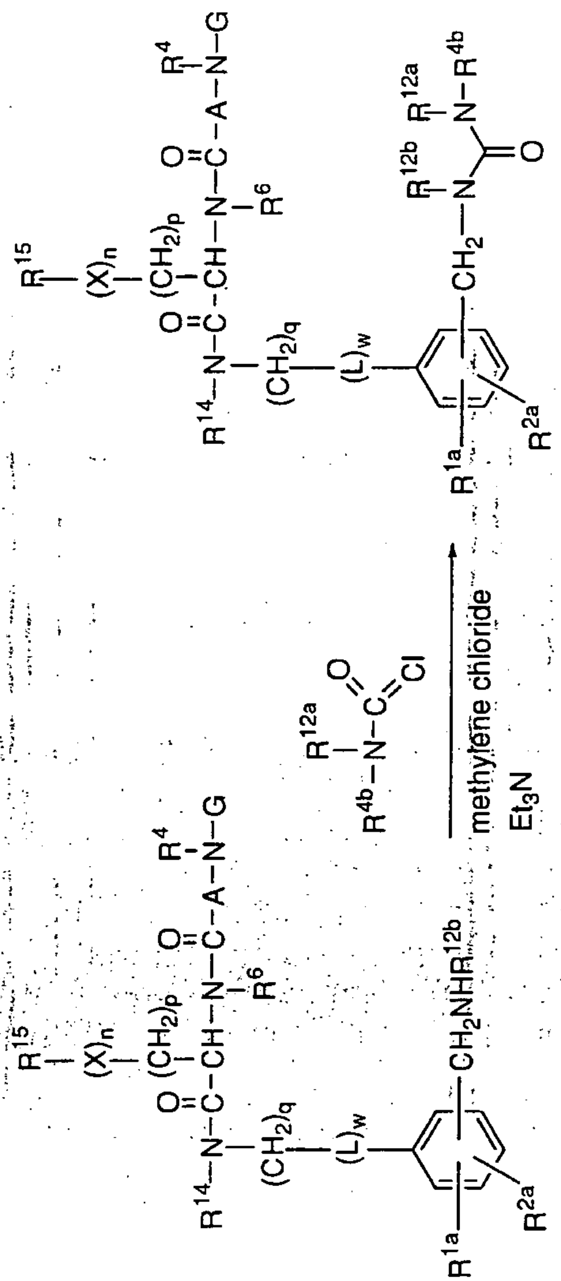
SCHEME 22



53

54

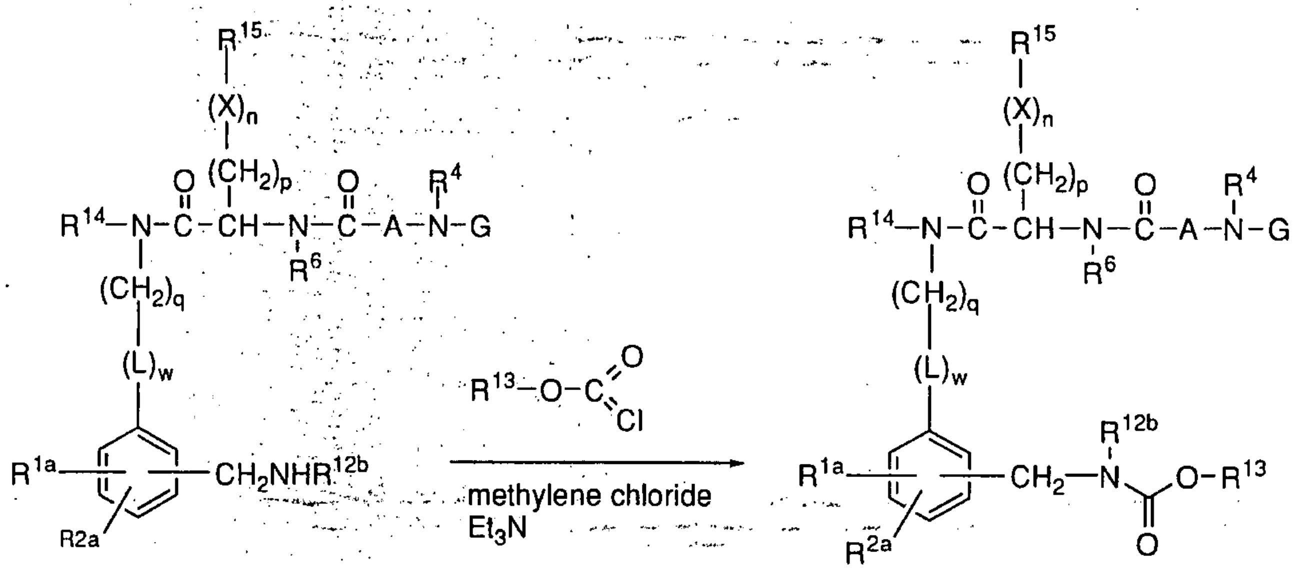
SCHEME 22 (CONT'D)



53

55

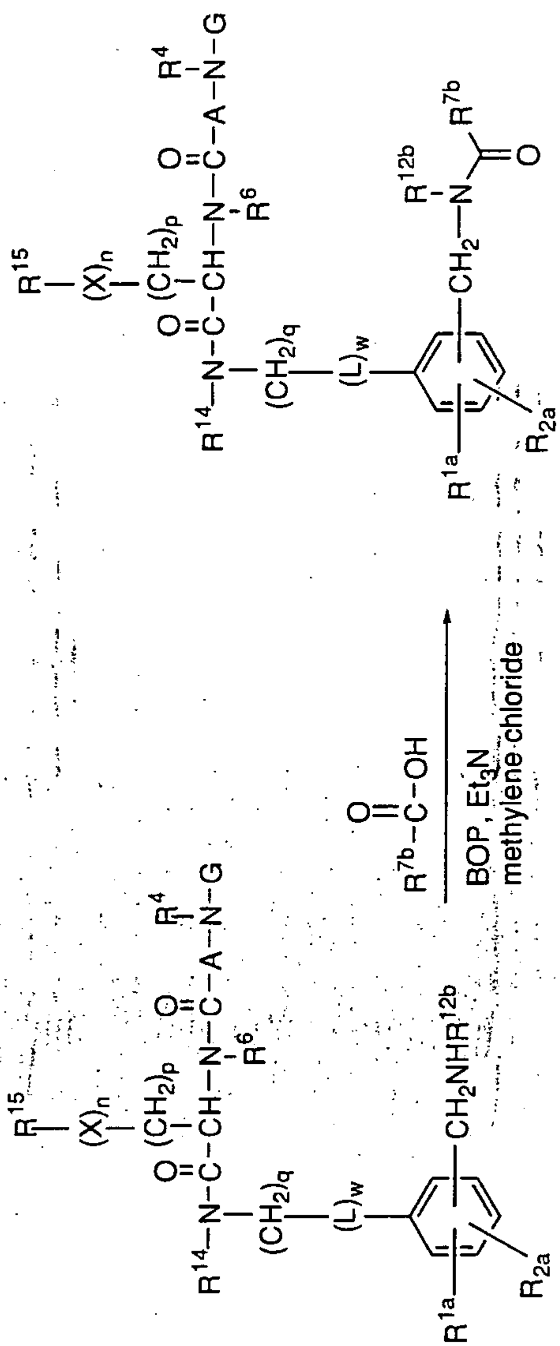
SCHEME 22 (CONT'D)



53 56

G is benzyloxycarbonyl

SCHEME 22 (CONT'D)



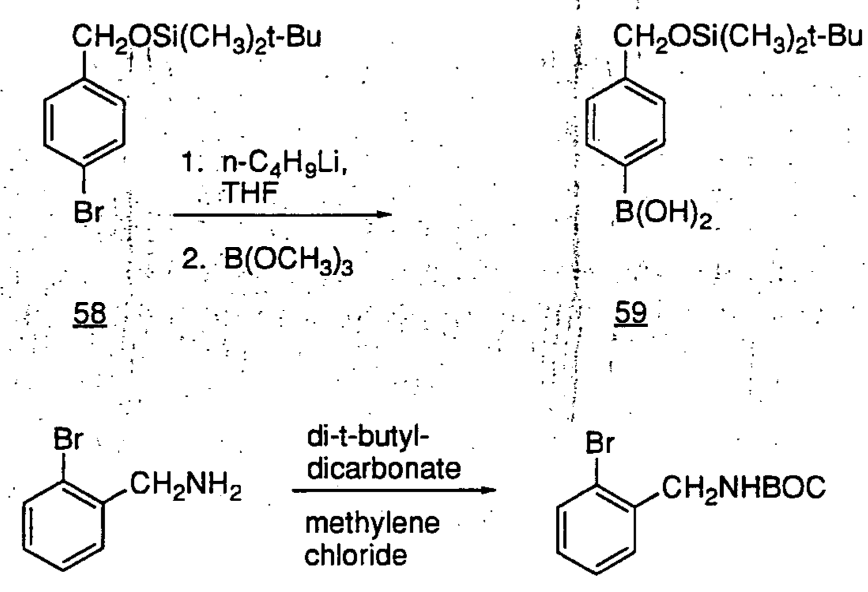
53

57

G is benzyloxycarbonyl

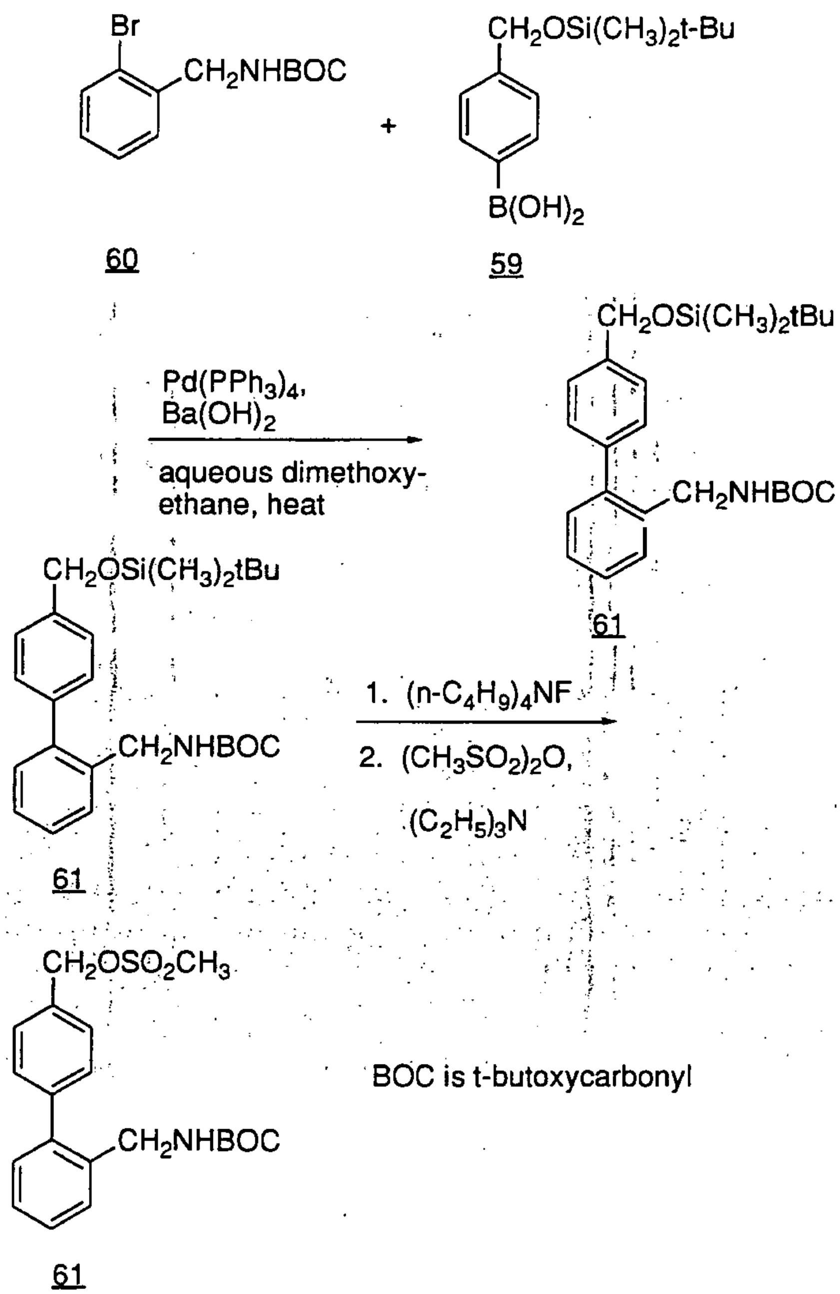
A useful preparation of the protected benzylamine intermediate 62 is shown in Scheme 23. Metallation of 4-bromobenzyl t-butyldimethylsilylether 58 with n-butyllithium followed by treatment with trimethyl borate gives the aryl boronic acid 59. Reaction of 59 with 2-bromo-N-(t-butoxycarbonyl)benzylamine 60 in the presence of tetrakis(triphenylphosphine)palladium(0) and barium hydroxide in aqueous 1,2-dimethoxyethane at elevated temperature gives the coupled product 61 in good yield. Desilylation is carried out by treatment with tetra-n-butylammonium fluoride; conversion to the O-methanesulfonate 62 is achieved by reaction of the intermediate benzyl alcohol with methanesulfonic anhydride. Conversion to the requisite amine derivative V is achieved by the procedure described in Scheme 5.

SCHEME 23



60

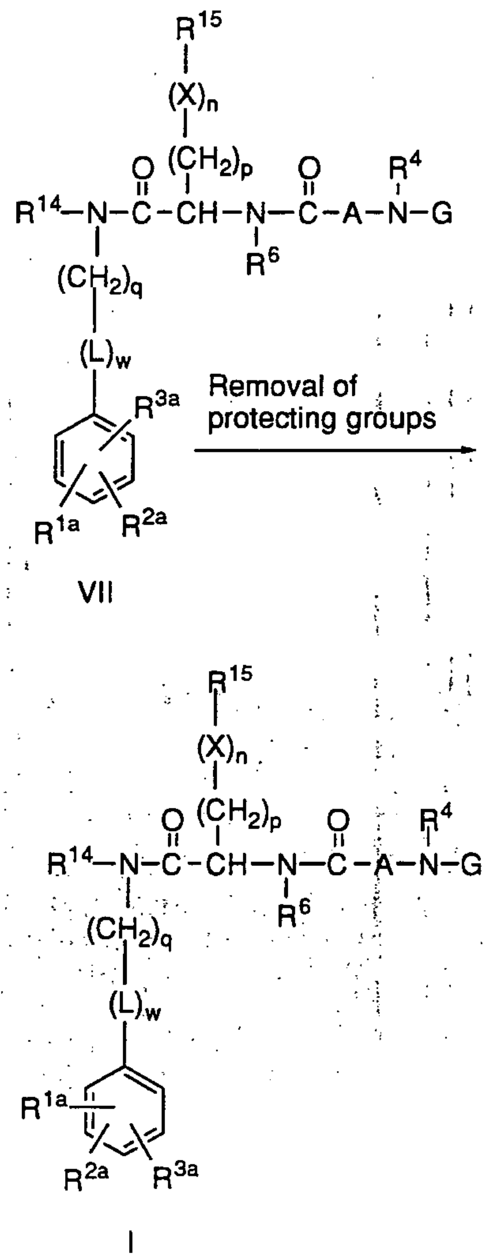
SCHEME 23 (Cont'd)



BOC is t-butoxycarbonyl

Conversion to the final products of formula I wherein R^5 is hydrogen, is carried out by simultaneous or sequential removal of all protecting groups from intermediate VII as illustrated in Scheme 24. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a platinum or palladium catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxycarbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Catalytic hydrogenation is also employed in the removal of N-triphenylmethyl (trityl) protecting groups. Removal of t-butoxy-carbonyl (BOC) protecting groups is carried out by treatment of a solution in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Protective Groups in Organic Synthesis.

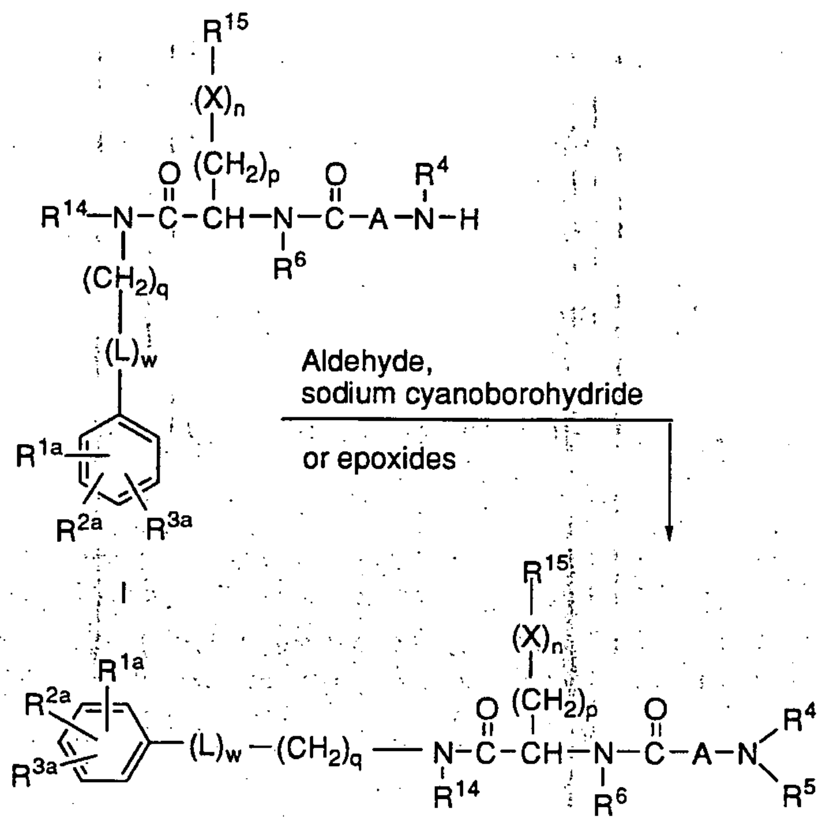
SCHEME 24



Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an

aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides as shown in Scheme 25. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatography (HPLC) or by recrystallization.

SCHEME 25



I

It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

The growth hormone releasing compounds of Formula I are useful in vitro as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, pinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., bombesin; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals. In addition, these compounds can be administered to humans in vivo as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered in vivo to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly

determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the disclosed novel substituted dipeptide analogs is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2. A still further use of the disclosed novel substituted dipeptide analogs is in combination with $\alpha 2$ adrenergic agonists or $\beta 3$ adrenergic agonists in the treatment of obesity or in combination with parathyroid hormone or bisphosphonates, such as MK-217 (alendronate), in the treatment of osteoporosis.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; Prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune

system, treatment of retardation, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting in growth retardation, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; Accelerating the recovery and reducing hospitalization of burn patients; Treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushings syndrome; Induction of pulsatile growth hormone release; Replacement of growth hormone in stressed patients; Treatment of osteochondrodysplasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; Attenuation of protein catabolic response after a major operation; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS. Treatment of hyperinsulinemia including nesidioblastosis; Adjuvant treatment for ovulation induction; To stimulate thymic development and prevent the age-related decline of thymic function; Treatment of immunosuppressed patients; Improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; Stimulation of osteoblasts, bone remodelling, and cartilage growth; Stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; Growth promotant in livestock; and stimulation of wool growth in sheep.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage

forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The

selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-butanamide, trifluoroacetate

Step A: 5-Phenyltetrazole

Zinc chloride (3.3 g, 24.3 mmol, 0.5 eq) was added to 15 mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0 g of benzonitrile (48.5 mmol, 1.0 eq) followed by 3.2 g of sodium azide (48.5 mmol, 1.0 eq). The heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30 mL) was added and the mixture acidified by the addition of 5.1 mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15 mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38 g (43.7 mmol, 90%) of the product.

Step B: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0 g (34.2 mmol) of 5-phenyltetrazole in 55 mL of acetone was added 5.0 mL of triethylamine (3.6 g, 35.6 mmol, 1.04 eq). After 15 minutes, a solution of 10.0 g of triphenylmethyl chloride (35.9 mmol, 1.05 eq) in 20 mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour.

Water (75 mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75 mL of water and dried at 60°C under vacuum to give 13.3 g (34.2 mmol, 100%) of the product.

Step C: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)]tetrazole

A solution of zinc chloride (6.3 g, 46.2 mmol, 0.6 eq) in 35 mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0 g, 77.3 mmol, 1.0 eq) was dissolved in 300 mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5 mL of 1.6 M n-butyllithium in hexane (80.0 mmol, 1.05 eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature.

In a separate flask, 4-iodotoluene (20.17 g, 92.5 mmol, 1.2 eq) and bis(triphenylphosphine)nickel(II)dichloride (1.5 g, 2.3 mmol, 0.03 eq) were dissolved in 60 mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5 mL of 3.0 M solution of methylmagnesium chloride in tetrahydrofuran (4.5 mmol, 0.06 eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10 mL of glacial acetic acid (1.6 mmol, 0.02 eq) in 60 mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150 mL of 80% saturated aqueous sodium chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150 mL of 80% saturated aqueous sodium chloride buffered to pH >10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to

approximately 50 mL then 250 mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50 mL and acetonitrile added to make the final volume 150 mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50 mL of cold acetonitrile followed by 150 mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0 g (62.8 mmol, 81%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.28 (s,3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Step D: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen4-yl)]tetrazole

A solution of 3.15 g (6.6 mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)]tetrazole in 25 mL of methylene chloride was treated with 1.29 g (7.25 mmol, 1.1 eq) of N-bromosuccinimide, 80 mg (0.5 mmol, 0.07 eq) of AIBN, 200 mg of sodium acetate and 200 mg of acetic acid. The mixture was heated at reflux for 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed.the the total volume reduced to approximately 12 mL and 12 mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81 g (5.04 mmol, 76%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step E: N-Triphenylmethyl-5-[2-(4'-azidomethylbiphen-4-yl)]tetrazole

To 5.57 g (10 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)]tetrazole in 20 mL of dimethyl sulfoxide was added 614 mg (12.5 mmol, 1.25 eq) of pulverized lithium azide. The

reaction was stirred at room temperature for 4 hours, during which time a thick precipitate formed. The precipitated solids were collected by filtration and washed with methanol, water, and then methanol again, and dried under vacuum for 16 hours to yield 4.06 g (78%) of the product as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): 3.46 (s, 2H), 6.82-7.55 (m, 22H), 7.95 (m, 1H).

Step F: N-Triphenylmethyl-5-[2-(4'-aminomethylbiphen-4-yl)]tetrazole

To a solution of 4.06 g (7.8 mmol) of N-triphenylmethyl-5-[2-(4'azidomethylbiphen-4-yl)]-tetrazole in 15 mL of tetrahydrofuran was added 2.05 g (7.8 mmol, l eq) of triphenylphosphine in small portions. The mixture was stirred at room temperature for 2 hours, at which time 0.2 mL of water was added and the reaction mixture stirred for 16 hours. The reaction mixture was concentrated to dryness under vacuum and the crude product chromatographed on a silica flash column, eluting with chloroform, to give 1.5 g (3.03 mmol, 39%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.21 (br s, 2H), 3.75 (s, 2H), 6.80-7.94 (m, 22H), 7.94 (m, 1H).

Step G: (R)-α-[t-Butoxycarbonylamino]-N-[[2'-(N-triphenyl-methyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-butanamide

To a solution of 30.5 mg (0.11 mmol) of N-BOC-D-homophenylalanine in 1 mL of methylene chloride at room temperature under a nitrogen atmosphere was added 54 mg (0.11 mmol, l eq) of N-triphenylmethyl-5-[2-(4'aminomethylbiphen-4-yl)]tetrazole (Step F), 25 mg (0.13 mmol, 1.2 eq) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 13 mg (0.13 mmol, 1.2 eq) of triethylamine. The reaction was stirred at room temperature for 16 hours, then transferred to a separatory funnel and washed with 2 mL of 5% aqueous citric acid and 2 mL of saturated aqueous sodium bicarbonate. The organic layer was removed, dried over magnesium sulfate, filtered and evaporated to dryness under vacuum. The residue was chromato-

graphed on a silica flash column, eluting with hexane/ethyl acetate (5:1), to give 29 mg (35%) of the product. [1]H NMR (200 MHz, $CDCl_3$): 1.43 (s, 9H), 2.05 (m, 2H), 2.67 (t, 8Hz, 2H), 4.05 (m, 1H), 4.32 (m, 1H), 4.99 (m, 1H), 6.19 (m, 1H), 6.78-7.15 (m, 27H), 7.95 (m, 1H).

Step H: (R)-α-[t-Butoxycarbonylamino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzene-butanamide

A solution of 29 mg (0.038 mmol) of the intermediate obtained in Step G in 1 mL of methanol was hydrogenated at room temperature and one atmosphere over 4 mg of 20% palladium hydroxide on carbon for two hours. The reaction mixture was then filtered through Celite to remove the catalyst, the solvent removed under vacuum and the residue flash chromatographed on silica to yield 19 mg (95%) of the title compound. [1]H NMR (200 MHz, CD_3OD): 1.43 (s, 9H), 1.95 (m, 2H), 2.64 (m, 2H), 4.00 (m, 1H), 4.34 (t, 5Hz, 2H), 7.00-7.30 (m, 8H), 7.50 (m, 5H). FAB-MS: calculated for $C_{29}H_{32}N_6O_3$ 512; found 513 (M+1, 24%).

Step I: (R)-α-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4yl]methyl]-benzenebutanamide, hydrochloride

A solution of 19 mg (0.037 mmol) of the intermediate obtained in Step H in 1 mL of methanol was treated with one drop of concentrated hydrochloric acid. The mixture was stirred at room temperature for 16 hours then evaporated to dryness under vacuum. The crude product was purified on reverse phase HPLC on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid [linear gradient: 60% methanol to 80% methanol over 10 minutes], to yield 14 mg (84%) of the product. [1]H NMR (200 MHz, CD_3OD): 2.11 (m, 2H), 2.64 (m, 2H), 3.89 (t, 6Hz, 1H), 4.42 (s, 2H), 7.05-7.32 (m, 8H), 7.58 (m, 5H). FAB-MS: calculated for $C_{24}H_{24}N_6O$ 412; found 413 (M+1,100%).

Step J: 2,2-Dimethylbutanedioic acid, 4-methyl ester

2,2-Dimethylsuccinic acid (20 g, 137 mmol) dissolved in 200 mL of absolute methanol at 0°C was treated dropwise with 2 mL of

concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stir for 16 hours. The mixture was concentrated under vacuum to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of the product as a viscous oil that slowly solidified upon standing. ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (s, 6H), 2.60 (s, 2H), 3.65 (s, 3H).

Step K: 3-Benzyloxycarbonylamino-3-methylbutanoic acid, methyl ester

To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester in 150 mL of benzene was added 13 mL of triethylamine (9.4 g, 93 mmol) followed by 21.8 mL of diphenylphosphoryl azide (27.8 g, 101 mmol). The mixture was heated under nitrogen at reflux for 45 minutes then 19 mL (19.9 g, 184 mmol) of benzyl alcohol was added and refluxing continued for 16 hours. The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL of ethyl acetate, washed with water, saturated aqueous sodium bicarbonate (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume under vacuum. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27 g (68.9 mmol, 75%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H).

Step L: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27 g (68.9 mmol) of 3-benzyloxycarbonylamino-3-methylbutanoic acid methyl ester in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2N NaOH (102 mmol). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0°C and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26 g (68.7 mmol, 99%) of the product. ^1H NMR (200 MHz, $CDCl_3$): 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

Step M: 3-Benzyloxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester

A solution of 2.93 g (11.7 mmol, 0.85 eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid in 5 mL of methylene chloride at room temperature was treated with 1.61 g (14.0 mmol) of N-hydroxysuccinimide followed by 2.67 g (14.0 mmol, 1 eq) of 1(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction mixture was stirred for 16 hours then transferred to a separatory funnel, washed with water and dilute aqueous sodium bicarbonate. The organic layer was removed, dried over magnesium sulfate, filtered, and solvents removed under vacuum. The crude product was chromatographed on a silica flash column, eluting with hexane/ethyl acetate (1:1), to give 3.9 g (quantitative) of the product. ^1H NMR (200 MHz, $CDCl_3$): 1.51 (s, 6H), 2.80 (s, 4H), 3.12 (s, 2H), 5.13 (s, 2H), 7.37 (s, 5H). FAB-MS: calculated for $C_{17}H_{20}N_2O_6$ 348; found 349 (M+1, 40%).

Step N: (R)-α-[(3-Benzyloxycarbonylamino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4yl]methyl]benzenebutanamide

A solution of 12 mg (0.023 mmol) of the intermediate obtained in Step I in 0.5 mL of methylene chloride at room temperature was treated with 9.2 mg (0.027 mmol, 1.2 eq) of 3-benzyloxy-carbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester (Step M) and 3.5 mg (0.027 mmol, 1.2 eq) of diisopropylethylamine. The reaction mixture was stirred at room temperature for 48 hours. Solvents were emoved under vacuum and the crude residue was purified on HPLC to give 14 mg of product. ^{1}H NMR (200 MHz, CD_3OD): 1.29 (s, 3H), 1.36 (s, 3H), 1.90 (m, 3H), 2.45 (m, 3H), 4.31 (m, 1H), 4.72 (d, 20Hz, 1H), 5.02 (d, 20Hz, 1H), 7.00-7.62 (m, 18H). FAB-MS: calculated for $C_{37}H_{39}N_7O_4$ 645; found 646 (M+1, 100%).

Step O: (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide, tri-fluoroacetate

A solution of 14 mg (0.21 mmol) of the intermediate obtained in Step N in 1 mL of methanol was hydrogenated at room temperature and one atmosphere over 1 mg of 20% palladium hydroxide on carbon for 16 hours. The reaction mixture was filtered through Celite and the filtrate concentrated under vacuum and the residue chromatographed on reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 65% methanol increased to 85% over 10 minutes), to give 10 mg (72%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.32 (s, 3H), 1.36 (s, 3H), 1.81 (m, 1H), 1.95 (m, 2H), 2.26 (m, 1H), 2.52 (s, 1H), 2.63 (m, 1H), 4.34 (m, 1H), 4.76 (d, 14Hz, 1H), 4.95 (d, 14Hz, 1H), 7.01-7.70 (m, 13H). FAB-MS: calculated for $C_{29}H_{33}N_7O_2$ 511; found 512 (M+1, 100%).

EXAMPLE 2

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzene-propanamide, trifluoroacetate

The title compound was prepared from N-BOC-D-phenylalanine by the methods described in Example 1. ^{1}H NMR (200 MHz, $CDCl_3$): 1.27 (s, 3H), 1.40 (s, 3H), 2.49 (d, 15Hz, 1H), 2.62 (d, 15Hz, 1H), 3.10 (m, 2H), 4.44 (m, 2H), 4.80 (m, 1H), 7.16 (s, 4H), 7.35 (s, 5H); 7.70 (m, 4H). FAB-MS: calculated for $C_{28}H_{31}N_7O_2$ 497; found 498 (M+1,100%).

EXAMPLE 3

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

Step A: (R)-α-[t-Butoxycarbonylamino]-N-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide

Prepared from N-triphenylmethyl-5-[2-(4'-aminomethyl-biphen-4-yl)]tetrazole and N_{im}-formyl-N_{α}-BOC-D-tryptophan by the procedure described in Example 1, Step G. ^{1}H NMR (200 MHz, $CDCl_3$): 1.40 (s, 9H), 3.18 (br s, 2H), 4.24 (br s, 2H), 4.48 (m, 1H), 5.24 (s, 1H), 6.28 (s, 1H), 6.70-7.70 (m, 27H), 7.90 (m, 1H), 8.82 (br s, 1H).

Step B: (R)-a-[t-Butoxycarbonylamino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step H. ^{1}H NMR (200 MHz, CD_3OD): 1.38 (s, 9H), 3.14 (m, 3H), 6.90-7.70 (m, 13H), 9.02 (br s, 1H). FAB-MS: calculated for $C_{30}H_{31}N_7O_4$ 553; found 554 (M+1,40%).

Step C: (R)-α-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyll-4-yl]methyl]-(N_{im}-formyl)indole-3-propanamide, trifluoroacetate

A solution of 80 mg (0.14 mmol) of the intermediate obtained in Step B in 4 mL methylene chloride was treated with 1 mL of anisole followed by 4 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 hour, then all volatiles were removed under vacuum. The residue was purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (45:55), to give 64 mg (77%) of the product. ^{1}H NMR (200 MHz, CD_3OD): 3.26 (m, 2H), 4.11 (t, 6Hz, 1H), 4.28 (m, 2H), 6.99 (s, 4H), 7.28-7.70 (m, 9H), 8.75 (br s, 1H). FAB-MS: calculated for $C_{26}H_{23}N_7O_2$ 465; found 466 (M+1, 22%).

Step D: 4,4-Dimethylazetidin-2-one

A 3-neck 3L round bottom flask equipped with a magnetic stirrer, thermometer, cold finger condenser and nitrogen bubbler was charged with 1L of ether. The flask was cooled to -65°C and into it was condensed 500-600 mL of isobutylene. The cold finger condenser was replaced with a dropping funnel and 200 mL (325 g, 2.30 mol) of chlorosulfonyl isocyanate was added dropwise over 1.5 hours. The mixture was maintained at -65°C for 1.5 hours then the dry ice/acetone cooling bath replaced with methanol/ice and the internal temperature slowly increased to -5°C at which time the reaction initiated and the internal temperature rose to 15°C with evolution of gas. The internal temperature remained at 15°C for several minutes then dropped back down to -5°C and the mixture stirred at -5°C for 1 hour. The methanol/ice bath was removed and the reaction mixture warmed to room temperature and stirred overnight.

The reaction mixture was transferred to a 3-neck 12L round bottom flask fitted with a mechanical stirrer and diluted with 2L of ether. The well-stirred reaction mixture was treated with 2L of saturated aqueous sodium sulfite. After 1 hour, an additional 1L of

saturated aqueous sodium sulfite was added followed by sufficient sodium bicarbonate to adjust the pH to approximately 7. The mixture was stirred another 30 minutes then the layers allowed to separate. The ether layer was removed and the aqueous layer reextracted with 2 x 1L of ether. The combined ether extracts were washed once with 500 mL of saturated aqueous sodium bicarbonate and once with 500 mL of saturated aqueous sodium chloride. The ether layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum to give 33 g of a pale yellow oil. The aqueous layer was made basic by the addition of solid sodium bicarbonate and extracted with 3 x 1L of ether. The combined ether extracts were washed and dried as described above, then combined with the original 33 g of pale yellow oil and concentrated under vacuum to give 67.7 g of product. Further extraction of the aqueous layer with 4 x 1L of methylene chloride and washing and drying as before gave an additional 74.1 g of product. Still further extraction of the aqueous layer with 4 x 1L of methylene chloride gave an additional 21.9 g of product. The combined product (163.7 g, 1.65 mol, 72%) was used in Step E without purification. ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (s, 6H), 2.75 (d, 3Hz, 2H), 5.9 (br s, 1H).

Step E: N-(t-Butoxycarbonyl)-4,4-dimethylazetidin-2-one

A 5L, 3-neck round bottom flask equipped with a magnetic stirrer, thermometer, nitrogen bubbler and addition funnel was charged with 88.2 g (0.89 mol) of 4,4-dimethylazetidin-2-one, 800 mL of methylene chloride, 150 mL of triethylamine (1.08 mol) and 10.9 g (0.089 mol) of 4-dimethylaminopyridine. To the stirred solution at room temperature was added dropwise over 15 minutes a solution of 235 g (1.077 mol) of di-t-butyl-dicarbonate in 300 mL of methylene chloride. The reaction mixture was stirred at room temperature overnight then diluted with 1L of methylene chloride and washed with 500 mL of saturated aqueous ammonium chloride, 500 mL of water, and 500 mL of saturated aqueous sodium chloride. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated

under vacuum to afford 180.3 g of crude product as an orange solid. The material was used directly in Step F without purification.
^{1}H NMR (200 MHz, $CDCl_3$): 1.50 (s, 9H), 1.54 (s, 6H), 2.77 (s, 2H).

Step F: 3-t-Butoxycarbonylamino-3-methylbutanoic acid

A 3L, 3-neck round bottom flask equipped with a magnetic stirrer, thermometer, nitrogen bubbler and addition funnel was charged with 180.3 g (0.89 mol) of N-(t-butoxycarbonyl)-4,4-dimethylazetidin-2-one dissolved in 1L of tetrahydrofuran. The solution was cooled to 0-5°C and treated dropwise with 890 mL of 1.0M aqueous lithium hydroxide over 30 minutes. The reaction mixture was stirred at 0-5°C for 2 hours then diluted with 1L of ether and 1L of water. The layers were allowed to separate and the aqueous layer was reextracted with an additional 1L of ether. The aqueous layer was acidified by the addition of 1L of saturated aqueous sodium bisulfate, then extracted with 1 x 1L and 2 x 500 mL of ether. The combined organic layer and ether extracts were washed with 500 mL of saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated under vacuum to give 173 g of a yellow oil that solidified upon standing. The material was slurried with warm hexane then filtered and dried under high vacuum to afford 168.5 g (0.775 mol, 87%) of product as a white solid.
^{1}H NMR (200 MHz, $CDCl_3$): 1.39 (s, 6H), 1.44 (s, 9H), 2.72 (s, 2H).
FAB-MS: calculated for $C_{10}H_{19}NO_4$ 217; found 218 (M+H, 54%).

Step G: (R)-α-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-(N_{im}-formyl)-indole-3-propanamide

A solution of 64 mg (0.11 mmol) of the intermediate obtained in Step C in 1 mL of methylene chloride at 0°C was treated with 25 mg (0.12 mmol, 1.1 eq) of dicyclohexylcarbodiimide and the resulting solution stirred at 0°C for 30 minutes. A solution of 53 mg (0.24 mmol, 2 eq) of 3-t-butoxycarbonylamino-3-methylbutanoic acid and 12 mg (0.12 mmol, 0.017 mL, 1.1 eq) of triethylamine in 1 mL of methylene chloride was added and the mixture stirred for 5 hours at

room temperature. The reaction mixture was evaporated to dryness under vacuum and the residue was dissolved in 1 mL of anisole and treated with 4 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 30 minutes the concentrated under vacuum. The residue was taken up in methanol and the solids removed by filtration. The filtrate was concentrated under vacuum; the residue was purified by reverse phase high pressure liquid chromatography on C18 to yield 31 mg (42%) of the product. ^{1}H NMR (200 MHz, CD_3OD): 1.14 (s, 3H), 1.25 (s, 3H), 2.37 (d, 15Hz, 1H), 2,48 (d, 15Hz, 1H), 3.11 (m, 2H), 4.26 (m, 2H), 4.72 (m, 1H), 6.92-7.70 (m, 13H), 8.55 (br s, 1H). FAB-MS: calculated for $C_{31}H_{32}N_8O_3$ 564; found 565 (M+1, 80%).

Step H: (R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

A solution of 31 mg (0.046 mmol) of the intermediate obtained in Step G in 1 mL of methanol was treated with 0.2 mL of concentrated hydrochloric acid and the resulting mixture heated at 65°C for 1.5 hours. All volatiles were removed under vacuum and the residue purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (50:50), to give 20 mg (67%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.15 (s, 3H), 1.28 (s, 3H), 2.38 (d, 16Hz, 1H), 2.50 (d, 16Hz, 1H), 3.19 (m, 2H), 4.20 (d, 14Hz, 1H), 4.32 (d, 14Hz, 1H), 4.73 (t, 7Hz, 1H), 6.90-7.70 (m, 13H). FAB-MS: calculated for $C_{30}H_{32}N_8O_2$ 536; found 536 (70%).

EXAMPLE 4

(R)-2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-butanamide, trifluoroacetate

Step A: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-butanamide

Prepared from N-BOC-D-2-aminobutanoic acid and aniline by the method described in Example 1, Step G. ^{1}H NMR (200 MHz, $CDCl_3$): 1.00 (t, 6Hz, 3H), 1.45 (s, 9H), 1.82 (m, 2H), 4.30 (m, 1H), 5.59 (d, 7Hz, 1H), 7.00-7.62 (m, 5H), 8.90 (br s, 1H). FAB-MS: calculated for $C_{15}H_{22}N_2O_3$ 278; found 279 (M+1, 40%).

Step B: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-N-[[2'-(N-triphenylmethyl-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-butanamide

A solution of 70 mg (0.25 mmol) of (R)-2-(t-butoxy-carbonylamino)-N-phenyl-butanamide in 0.5 mL of dry dimethyl-formamide was treated with 10 mg (0.25 mmol, 1 eq) of 60% sodium hydride oil dispersion. The mixture was stirred at room temperature for 20 minutes, then treated with a solution of 140 mg (0.25 mmol, 1 eq) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)]tetrazole (Example 1, Step D) in 0.5 mL of dry dimethylformamide. The mixture was stirred at room temperature for 2 hours, then quenched by the addition of 2 mL of water. The mixture was extracted several times with ethyl acetate; the combined extracts were washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate then dried over magnesium sulfate, filtered and the filtrate dried under vacuum. The crude material was chromatographed on a flash silica column, eluting with hexane/ethyl acetate (1:1), to give 91 mg (48%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 0.74 (t, 6Hz, 3H), 1.32 (s, 9H), 1.58 (m, 2H), 4.20 (m, 1H), 4.79 (s, 2H), 6.82-7.60 (m, 27H), 7.86 (m, 1H).

Step C: (R)-2-(t-Butoxycarbonylamino)-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]butanamide

Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step H. ^{1}H NMR (200 MHz, $CDCl_3$): 0.74 (t, 6Hz, 3H), 1.36 (s, 9H), 1.55 (m, 2H), 4.13 (m, 1H), 4.70 (d, 14Hz, 1H), 5.02 (d, 14Hz, 1H), 5.22 (m, 1H), 7.00-7.62 (m, 12H), 8.01 (m, 1H). FAB-MS: calculated for $C_{29}H_{32}N_6O_3$ 512; found 513 (M+1, 100%).

Step D: (R)-2-Amino-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,l'-biphenyl]-4-yl]methyl]butanamide, hydrochloride

Prepared from the intermediate obtained in Step C by the method described in Example 1, Step I. ^{1}H NMR (200 MHz, CD_3OD): 0.83 (t, 7Hz, 3H), 1.68 (m, 2H), 3.80 (m, 1H), 4.81 (d, 14Hz, 1H), 5.01 (d, 14Hz, 1H), 7.00-7.70 (m, 13H). FAB-MS: calculated for $C_{24}H_{24}N_{6}0$ 412; found 413 (M+1, 100%).

Step E: 3-t-Butoxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 3, Step F) and N-hydroxysuccinimde by the procedure describe in Example 1, Step M. ^{1}H NMR (200 MHz, $CDCl_3$): 1.41 (s, 9H), 1.43 (s, 6H), 2.82 (s, 4H), 3.07 (s, 2H), 4.72 (br s, 1H).

Step F: (R)-2-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)-amino]-N-phenyl-N-[[2'-(1H-tetra-zol-5-yl)[1,1'-biphenyl]-4yl]methyl]-butanamide

Prepared as in Example 1, Step N from (R)-2-amino-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,l'-biphenyl]-4-yl]methyl]butanamide, hydrochloride and 3-t-butoxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester. ^{1}H NMR (200 MHz, CD_3OD): 0.74 (t, 7Hz, 3H), 1.32 (s, 6H), 1.40 (s, 9H), 1.58 (m, 2H), 2.45 (d, 13Hz, 1H), 2.58 (d, 13Hz, 1H), 4.29 (m, 1H), 4.78 (d, 14Hz, 1H), 4.95 (d, 14Hz, 1H), 6.97-7.79 (m, 13H). FAB-MS: calculated for $C_{34}H_{41}N_{7}0_{4}$ 611; found 612 (M+1, 100%).

Step G: (R)-2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-phenyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 3, Step H. ^{1}H NMR (200 MHz, CD_3OD): 0.72 (t, 7Hz, 3H), 1.32 (s, 3H), 1.40 (s,

3H), 1.58 (m, 2H), 2.51 (m, 2H), 4.28 (m, 1H), 4.73 (d, 14Hz, 1H), 4.99 (d, 14Hz, 1H), 6.95-7.83 (m, 13H). FAB-MS: calculated for $C_{29}H_{33}N_7O_2$ 511; found 512 (M+1, 100%).

EXAMPLE 5

2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide, trifluoroacetate

Step A: 2-t-Butoxycarbonylamino-N-[[2'-(N-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]acetamide

Prepared from N-triphenylmethyl-5-[2-(4'-aminomethyl-biphen-4-yl)]tetrazole (Example 1, Step F) and N-BOC-glycine by the procedure described in Example 1, Step G. ^1H NMR (200 MHz, $CDCl_3$): 1.43 (s, 9H), 3.72 (d, 5Hz, 2H), 4.32 (d, 6Hz, 2H), 5.06 (m, 1H), 6.30 (m, 1H), 6.82-7.68 (m, 22H), 7.95 (m, 1H).

Step B: 2-t-Butoxycarbonylamino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step H. ^1H NMR (200 MHz, CD_3OD): 1.42 (s, 9H), 3.69 (s, 2H), 4.38 (d, 6Hz, 2H), 6.90-7.28 (m, 4H), 7.42-7.69 (m, 4H). FAB-MS: calculated for $C_{21}H_{24}N_6O_3$, 408; found 409 (M+1, 20%).

Step C: 2-Amino-N-[[2'-(1H-tetrazol-5-yl)[1,1'-bi-phenyl]-4-yl]methyl]acetamide, hydrochloride

Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step I. ^1H NMR (200 MHz, CD_3OD): 3.84 (s, 2H), 4.35 (s, 2H), 7.10-7.83 (m, 8H). FAB-MS: calculated for $C_{16}H_{16}N_6O$ 308; found 309 (M+1, 100%).

Step D: 2-[(3-Benzyloxycarbonylamino-3-methyl-1-oxo-butyl)-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4yl]-methyl]acetamide

Prepared from the intermediate obtained in Step C and 3-benzyloxycarbonylamino-3-methylbutanoic acid, N-hydroxysuccinimide ester by the procedure described in Example 1, Step N. ^{1}H NMR (200 MHz, CD_3OD): 1.37 (s, 6H), 2.60 (s, 2H), 3.79 (s, 2H), 4.33 (s, 2H), 5.00 (s, 2H), 6.95-7.65 (m, 13H). FAB-MS: calculated for $C_{26}H_{33}N_7O_4$ 507; found 508 (M+1, 20%).

Step E: 2-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]acetamide, trifluoroacetate

Prepared from the intermediate obtained in Step D by the procedure described in Example 1, Step O. ^{1}H NMR (200 MHz, CD_3OD): 1.38 (s, 6H), 2.52 (s, 2H), 3.89 (s, 2H), 4.38 (s, 2H), 7.00-7.70 (m, 8H). FAB-MS: calculated for $C_{21}H_{25}N_7O_2$ 407; found 408 (M+1,100%).

EXAMPLE 6

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methyl-amino)carbonyl]amino][1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide, trifluoroacetate

Step A: N-(t-Butoxycarbonyl)-D-tryptophan benzyl ester

Finely divided t-butoxycarbonyl-D-tryptophan (3 g, 10 mmol) was suspended in methylene chloride and benzyl alcohol (1.08 mL, 10 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) were added and stirred at room temperature. Solid 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.92 g, 10 mmol) was then added in three roughly equal portions over 5 minutes. The reaction mixture was stirred for 3 hours at room temperature during which time the reaction mixture became a homogeneous solution. The reaction

mixture was poured into water (100 mL) and extracted with methylene chloride (2 x 50 mL). The combined methylene chloride layers were washed with 5% aqueous citric acid solution (100 mL) and 5% aqueous sodium bicarbonate solution (100 mL). The resulting methylene chloride layer was dried over magnesium sulfate, filtered and evaporated under vaccum to give an off-white solid. This solid material was chromatographed on silica gel using ethyl acetate/hexanes (2:3 v/v) as eluant. This afforded 3.56 g (91%) of the desired benzyl ester as a white amorphous powder.
^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (s, 9H), 3.27 (d, 2H), 4.69 (m, 1H), 5.17 (ABq, 2H), 6.78 (br s, 1H), 7.15-7.42 (m, 8H), 7.53 (d, 1H), 7.97 (br s, 1H).

Step B: D-Tryptophan benzyl ester

N-(t-Butoxycarbonyl)-D-tryptophan benzyl ester (3.5 g, 8.87 mmol) was dissolved in methylene chloride (10 mL) and stirred at room temperature and trifluoroacetic acid (20 mL) was added dropwise to the ester. The reaction mixture was stirred at room temperature for one hour during which time the reaction darkened. The reaction mixture was directly evaporated under vacuum to give a white solid. This solid was dissolved in chloroform (100 mL) and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with chloroform (2 x 25 mL) and the combined chloroform layers were dried over potassium carbonate. Filtration and concentration of the chloroform solution under vacuum gave a pale yellow oil (3.14 g, 82%) which was mainly the desired product.
^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (s, 9H), 3.09 (dd, 1H), 3.27 (dd, 1H), 3.88 (m, 1H), 5.10 (s, 2H), 6.93 (br s, 1H), 7.15-7.39 (m, 8H), 7.59 (d, 1H), 8.03 (br s, 1H).

Step C: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-1H-indole-3-propanoic acid, benzyl ester

Crude D-tryptophan benzyl ester (1.0 g, 3.40 mmol), 1-hydroxybenztriazole hydrate (0.63 g, 4.1 mmol) and t-butoxycarbonyl-

α-methylalanine (0.84 g, 4.11 mmol) were stirred together at room temperature in chloroform (20 mL). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (980 mg, 5.11 mmol) was added to this mixture in a single portion. The reaction mixture was stirred at room temperature for 4 hours and worked up by pouring into water (50 mL). The chloroform layer was separated and washed with 5% aqueous citric acid solution (25 mL) and 5% aqueous sodium bicarbonate solution (25 mL). The chloroform layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a thick oily foam. Chromatography on silica gel using ethyl acetate/hexanes (2:3 v/v) afforded a yellow foam (0.822 g 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (s, 9H), 1.39 (s, 6H), 3.29 (m, 2H), 4.88 (m, 1H), 5.03 (s, 2H), 6.88 (br s, 1H), 7.05-7.35 (m, 8H), 8.53 (d, 1H), 7.98 (br s, 1H).

Step D: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-1H-indole-3-propanoic acid

The benzyl ester (0.82 g, 1.71 mmol) obtained in Step C and 10% palladium on carbon (150 mg) were stirred together in ethyl acetate (5 mL). The solution was degassed and a hydrogen atmosphere introduced over the reactants using a balloon for 32 hours. The reaction products were isolated by filtering the reaction mixture through a Celite plug. The plug was washed with additional ethyl acetate (3 x 10 mL). The combined filtrates were evaporated under vacuum to afford the product (680 mg, 102%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (s, 9H), 1.41 (s, 6H), 3.32 (dd, 1H), 3.42 (m, 1H), 4.87 (br s, 1H), 6.82 (d, 1H), 7.13-7.35 (m, 8H), 7.60 (d, 1H), 8.28 (br s, 1H).

Step E: 4-Methyl-2'-nitro-1,1'-biphenyl

A vigorously stirred mixture of 34 g (0.25 mol) of 4-tolylboronic acid and 34 g (0.17 mol) of 2-bromo-1-nitrobenzene in a mixture of 170 mL of 5N sodium hydroxide, 57 mL of water, 215 mL of 2-propanol and 1080 mL of benzene was treated with 11.9 g of

(tetrakis)triphenylphosphine palladium(0). The two-phase mixture was heated at reflux for three hours. The cooled reaction mixture was filtered through Celite and the filter cake washed with fresh benzene. The organic layer was separated and washed with water (3x), dried over magnesium sulfate and filtered. The filtrate was evaporated under vacuum and the residue (46.1 g) purified by preparative high pressure liquid chromatography on silica gel, eluting with hexane/ethyl acetate (20:1), to give 28.05 g of the product. ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (s, 3H), 7.20 (m, 4H), 7.43 (m, 2H), 7.59 (t, 1H), 7.8 (d, 1H). EI-MS: calculated for $C_{13}H_{11}NO_2$ 213; found 213 (M+).

Step F: 4-Bromomethyl-2'-nitro-1,1'-biphenyl

Prepared from 4-methyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step D. ^{1}H NMR (200 MHz, $CDCl_3$): 4.53 (s, 2H), 7.2-7.7 (m, 7H), 7.85 (m, 1H).

Step G: 4-Azidomethyl-2'-nitro-1,1'-biphenyl

Prepared from 4-bromomethyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step E. ^{1}H NMR (200 MHz, $CDCl_3$): 4.39 (s, 2H), 7.2-7.7 (m, 7H), 7.85 (d, 1H).

Step H: 4-Aminomethyl-2'-nitro-1,1'-biphenyl

Prepared from 4-azidomethyl-2'-nitro-1,1'-biphenyl by the procedure described in Example 1, Step E. ^{1}H NMR (200 MHz, $CDCl_3$): 3.90 (s, 2H), 7.2-7.7 (m, 7H), 7.83 (d, 1H).

Step I: (R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[(2'-nitro)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide

The acid (338 mg, 0.87 mmol) from Step D and 4-aminomethyl-2'-nitro-1,1'-biphenyl (200 mg, 0.87 mmol) and triethylamine (0.245 mL, 1.76 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature. Benzotriazolyl-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (388 mg,

0.87 mmol) was added in a single portion. The reaction mixture was stirred togerther for 3.5 hours then the reaction was quenched by adding saturated aqueous sodium chloride (10 mL) and extracted with methylene chloride (3 x 20 mL). The combined extracts were dried over magnesium sulfate, filtered and evaporated under vacuum. The resulting thick gum was chromatographed on silica gel using ethyl acetate/hexanes (1:2 v/v) to give 297 mg (50%) of an orange semi-solid. ^{1}H NMR (400 MHz, CD_3OD): 1.08 (s, 9H), 1.26 (s, 3H), 1.32 (s, 3H), 3.29 (dd, 1H), 3.43 (dd, 1H), 4.35 (m, 2H), 4.64 (m, 1H), 7.00-7.20 (m, 7H), 7.34 (d, 1H), 7.42 (m, 1H), 7.53 (t, 1H), 7.61 (d, 1H), 7.67 (t, 1H), 7.83 (d, 1H), 8.22 (s, 1H).

<u>Step J:</u> <u>(R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[(2'-amino)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide</u>

The amide (142 mg, 0.24 mmol) from Step I was dissolved in ethanol (5 mL) and 10% palladium on carbon (15 mg) was added. The ethanolic mixture was degassed and a hydrogen atmosphere introduced and maintained above the reaction mixture for 2.5 hours using a balloon. The hydrogenation catalyst was removed by filtration through a Celite pad. The pad was washed carefully with methylene chloride (4 x 5 mL). The combined filtrates were evaporated under vacuum to give a powdery white foam (124 mg, 92%). ^{1}H NMR (400 MHz, CD_3OD): 1.09 (s, 9H), 1.26 (s, 3H), 1.31 (s, 3H), 3.29 (m, 1H), 3.43 (dd, 1H), 4.36 (m, 2H), 4.62 (m, 1H), 6.87 (m, 2H), 7.00-7.45 (m, 10H), 7.60 (d, 1H), 8.20 (s, 1H). FAB-MS: calculated for $C_{33}H_{39}N_5O_4$ 569; found 570 (M+1).

<u>Step K:</u> <u>(R)-α-[(2-t-Butoxycarbonylamino-2-methyl-1-oxopropyl)-amino]-N-[[2'-[[(methylamino)-carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide</u>

The amine (25 mg, 0.04 mmol) from Step J was dissolved in methylene chloride and methyl isocyanate (0.009 mL, 0.15 mmol) was added to the amine. The reaction mixture was stirred together at

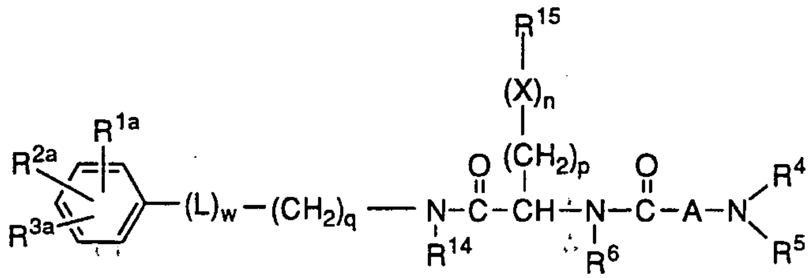
room temperature for 2.5 hours then the volatiles were removed directly under vacuum. The resultant residue was chromatographed on silica gel using ethyl acetate/hexanes (4:1 v/v) to afford the desired product (23 mg, 82%). ^{1}H NMR (200 MHz, CD_3OD): 1.10 (s, 9H), 1.24 (s, 3H), 1.30 (s, 3H), 2.64 (d, 3H), 3.33 (ABq, 2H), 4.33 (m, 2H), 4.60 (m, 1H), 6.23 (m, 1H), 6.96-7.45 (m, 11H), 7.58 (d, 1H), 7.68 (m, 1H), 8.20 (m, 1H). FAB-MS: calculated for $C_{35}H_{42}N_6O_5$ 626; found 627 (M+1).

Step L: (R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[(methylaminocarbonyl)amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide, trifluoroacetate

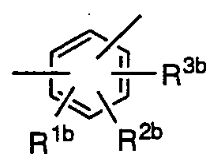
The intermediate obtained in Step K (15 mg, 0.023 mmol) and anisole (0.01 mL, 0.09 mmol) were dissolved in methanol (0.5 mL) and hexanes (0.5 mL). To this solution 0.5 mL of 9 N aqueous hydrochloric acid was added. The reactants were stirred at room temperature for 30 minutes then the hexane layer was removed using a pipette. The aqueous methanolic layer was evaporated at atmospheric pressure using a fast stream of nitrogen at room temperature. The solid material thus obtained was purified by reverse phase medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (85:15 v/v). This afforded 11.3 mg (0.018 mmol, 74%) of the title compound. ^{1}H NMR (400 MHz, CD_3OD): 1.38 (s, 3H), 1.56 (s, 3H), 2.66 (s, 3H), 3.18 (dd, 1H), 3.33 (dd, 1H), 4.35 (ABq, 2H), 4.78 (t, 1H), 6.98-7.47 (m, 10H), 7.62 (d, 1H), 7.64 (d, 1H). FAB-MS: calculated for $C_{30}H_{34}N_6O_3$ 526; found 527 (M+1).

WHAT IS CLAIMED IS:

1. A compound having the formula:



where L is



n is 0 or 1;
p is 0 to 6;
q is 0 to 4;
w is 0 or 1;

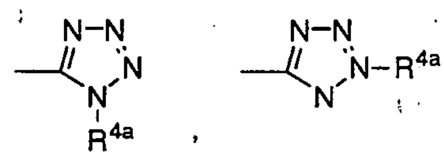
X is C=O, O, $S(O)_m$, $-\overset{\text{OH}}{\overset{|}{\text{CH}}}-$, $-\overset{\text{R}^{10}}{\overset{|}{\text{N}}}-$, -CH=CH-;
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_m$-R^{7a}, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, R^4R^5-$NCOO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy; R^{7a}

and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is



$R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, $R^{7b}CO(CH_2)_v$-, $R^{7b}O(CH_2)_vCO$-, $R^{4b}R^{12c}N(CH_2)_v$-, $R^{12a}R^{12b}NCO(CH_2)_v$-, $R^{12a}R^{12b}NCS(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CO(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CS(CH_2)_v$-, $R^{4b}R^{12a}NCON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NCSN(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CON(R^{12c})(CH_2)_v$-, $R^{4b}R^{12a}NN(R^{12b})CSN(R^{12c})(CH_2)_v$-, $^{4b}R^{12a}NN(R^{12b})$-COO-$(CH_2)_v$-, $R^{4b}R^{12a}NCOO(CH_2)_v$-, or $R^{13}OCON(R^{12c})(CH_2)_v$-, where v is 0 to 3;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12a} and R^{12c}, or R^{4b} and R^{12a}, or R^{4b} and R^{12a}, or R^{4b} and R^{12c}, or R^{13} and R^{12c}, can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3 and R^1 and R^{10} are as defined;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $-NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents

on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy where R^{10} and R^{11} are as defined;

R^{14} is hydrogen, R^1, R^2 independently disubstituted phenyl, C_1-C_{10} alkyl or substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl or $-NR^{10}R^{11}$ where R^1, R^2, R^{10} and R^{11} are as defined;

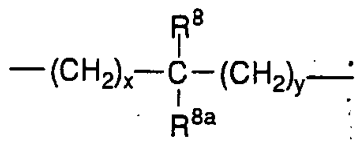
R^{15} is hydrogen, trifluoromethyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted naphthyl, C_3-C_7 cycloalkyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted naphthyl, R^1, R^2 independently disubstituted naphthyl C_1-C_3 alkoxy, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ or R^1, R^2 independently disubstituted heterocycle, where the heterocycle is imidazole, thiophene, furan, pyrrole, oxazole, thiazole, triazole, tetrazole, pyridine, benzofuran, benzothiophene, benzimidazole, indole, 7-azaindole, oxindole or indazole; where R^1, R^2, R^{10} and R^{11} are as defined above.

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl, C_1-C_5-

alkoxycarbonyl or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B, r, s, R^1, R^{10} as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

A is



where x and y are independently 0-3;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or

R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

n is 0 or 1;
p is 0 to 4;
q is 0 to 2;
w is 0 or 1;

X is O, $S(O)_m$, $-\overset{\overset{R^{10}}{|}}{N}-$, -CH=CH-;
m is 0 to 2;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9;

R^9 is as defined in Claim 1.

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a} or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR', O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl, phenyl C_1-C_6 alkyl or C_1-C_5 alkanoyl -C_1-C_6 alkyl.

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are hydroxy, $NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^{14} and R^{15} are as defined in Claim 1;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl or phenyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

R^4 and R^5 can be taken together to form $-(CH_2)_rB(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or N-R^{10}, r and s are independently 1 to 3 and R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

A is

$$-(CH_2)_x-\overset{\displaystyle R^8}{\underset{\displaystyle R^{8a}}{\overset{|}{\underset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl-C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 4; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein:

n is 0 or 1;
p is 0 to 3;
q is 0 to 2;
w is 0 or 1;
X is O, $S(O)_m$, -CH=CH-;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9 or phenoxy substituted with R^9;

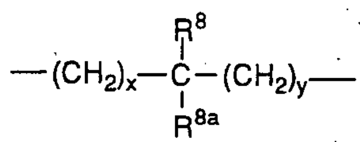
R^{12a}, R^{12b} and R^{12c} are independently R^{5a} or OR^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form $-(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above, and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^4, R^{4a}, R^{4b}, R^5 and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen or C_1-C_{10} alkyl;

A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; or R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 wherein:

n is 0 or 1;
p is 0 to 2;
q is 1;
w is 1;
X is O, $S(O)_m$ or -CH=CH-;
m is 0 or 1;

R^1, R^2, R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, -$S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl and v is 0 or 1;

R^{3a} and R^{3b} are independently hydrogen, R^9, or C_1-C_6 alkyl substituted with R^9;

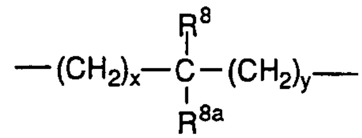
R^{12a}, R^{12b} and R^{12c} are independently R^{5a}. R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{13} and R^{12b} or R^{12a} and R^{4b} can be taken together to form -$(CH_2)_r$-B-$(CH_2)_s$- where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 2, R^1 is as defined above and R^{10} is hydrogen, C_1-C_6 alkyl or C_1-C_5 alkanoyl-C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^4, R^{4a}, R^{4b}, R^5, and R^{5a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_{20} alkanoyloxy, C_1-C_5 alkoxycarbonyl or carboxy;

R^6 is hydrogen;

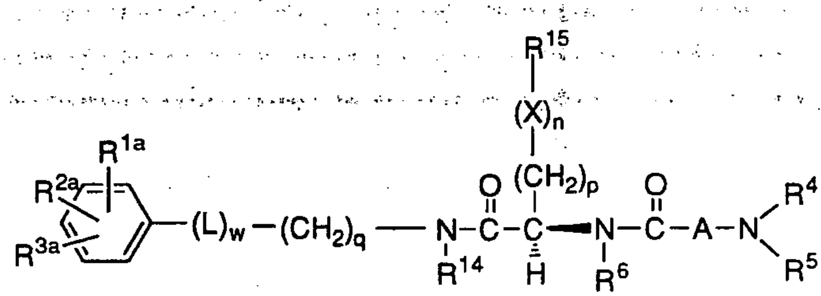
A is



where x and y are independently 0-1;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, R^1 substituted or R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

5. A stereospecific compound of Claim 1 having the following structural formula:



Ia

where X, n, p, q, L, w, R^{1a}, R^{2a}, R^{3a}, R^4, R^5, R^6, R^{14}, R^{15}, and A are as defined in Claim 1

6. A compound of Claim 1 which is:

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-4-phenylbutyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-4-phenylbutyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-5-phenylpentyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-5-phenylpentyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-(1H-indole-3-yl)propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[(phenylmethyl)oxy]propyl]amino]-methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[(phenylmethyl)-oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(3-Amino-3-methyl-1-oxobutyl)amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]propyl]-amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[(2-Amino-2-methyl-1-oxopropyl)-amino]-1-oxo-3-[[(2,6-difluorophenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxo-butyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide;

(R)-4'-[[[2-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-1-oxo-3-[[(2,6-difluoro-phenyl)methyl]oxy]-propyl]amino]methyl]-N-ethyl-[1,1'-biphenyl]-2-carboxamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methyl-amino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzene-butanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-a-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[(phenyl-methyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[(methylamino)carbonyl]-amino][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxy-methyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenebutanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-benzenepentanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]benzenepentanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-1H-indole-3-propanamide;

(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)-oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[(phenylmethyl)oxy]propanamide;

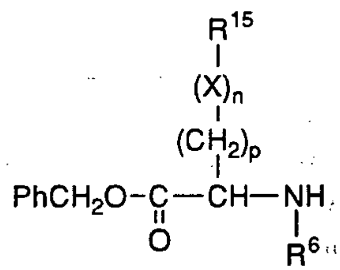
(R)-α-[(3-Amino-3-methyl-1-oxobutyl)amino]-N-[[2'-[[[(methyl-amino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)-methyl]oxy]propanamide;

(R)-α-[(2-Amino-2-methyl-1-oxopropyl)amino]-N-[[2'-[[[(methylamino)carbonyl]amino]methyl]-[1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluoro-phenyl)methyl]oxy]propanamide;

(R)-α-[[3-[2(R)-Hydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide; or

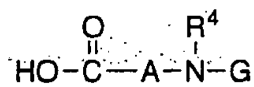
(R)-α-[[3-[2(S),3-Dihydroxypropyl]amino-3-methyl-1-oxobutyl]-amino]-N-[[2'-[[[(methylamino)carbonyl]-amino]methyl][1,1'-biphenyl]-4-yl]methyl]-3-[[(2,6-difluorophenyl)methyl]oxy]-propanamide.

7. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



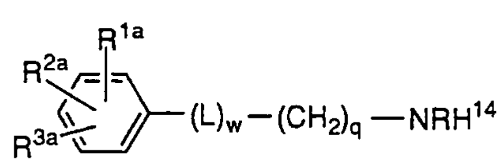
II

where R^6, R^{15}, X, n and p are as defined in Claim 1 with a compound having the formula:



III

where R^4 and A are defined in Claim 1 and G is a protecting group; which step is either followed by or preceded by the treatment of the compound with



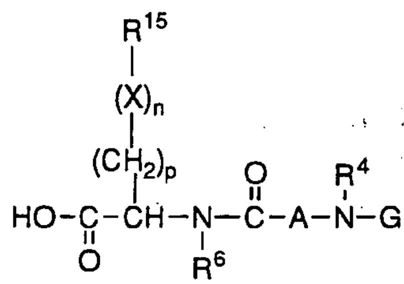
V

where R^{1a}, R^{2a}, R^{3a}, R^{14}, L, q and w are as defined in

Claim 1, followed by replacement of the protecting group G with R^5.

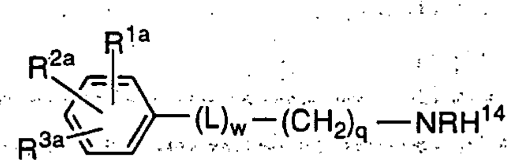
8. The process of Claim 7 where compound II is first reacted with compound III followed by reaction with compound V.

9. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:



IV

where R^4, R^6, R^{15}, A, X, n and p are as defined in Claim 1 and G is a protecting group, with a compound having the formula:



V

where R^{1a}, R^{2a}, R^{3a}, R^{14}, L, q and w are as defined in Claim 1, followed by replacement of the protecting group G with R^5.

10. The process of Claim 9 where the protecting group G is t-butoxycarbonyl or benzyloxycarbonyl.

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

12. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

13. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim I used in combination with other growth hormone secretagogues such as, GHRP-6 or GHRP-1, growth hormone releasing factor (GRF) or one of its analogs, IGF-1 or IGF-2, or B-HT920.

14. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1 in combination with an α_2-adrenergic agonist or β_3-adrenergic agonist.

15. A composition for the treatment of obesity which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an α_2-adrenergic agonist or β_3-adrenergic agonist.

16. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis an effective amount of a compound of Claim 1 in combination with parathyroid hormone or a bisphosphonate.

17. A composition for the treatment of osteoporosis which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with parathyroid hormone or a bisphosphonate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10551

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/00, 37/02, 37/36
US CL :514/002, 012, 021
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/002, 012, 021

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Int. J. Peptide Protein Res., Volume 38, issued 1991, K. Sato et al., "Solid Phase Synthesis of Human Growth Hormone-Releasing Factor Analogs Contianing a Bicyclic Beta-Turn Dipeptide", pages 340-345, see entire document.	1-17
A	Chem. Pharm. Bull., Volume 32, No. 3, issued 1984, N. Fujii et al., "Studies on Peptides. CXX. Synthesis of Growth Hormone Releasing Factor (GRF-37-NH2) and N-Biotinyl-GRF-44 NH2", pages 1200-1208, see entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
26 JANUARY 1994	04 FEB 1994

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